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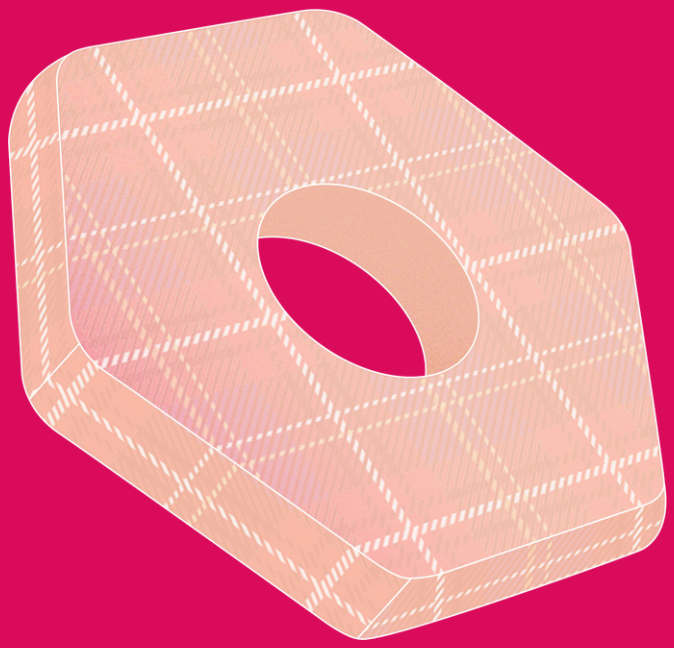

ABSTRACT BOOK

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OS-1-YI
Integrated characterisation of anti-tumour immunity following neoadjuvant immunotherapy of resectable hepatocellular carcinoma: final results of the PRIME-HCC study

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Background and aims:
Neoadjuvant immune checkpoint inhibition (ICI) is an emerging strategy in liver-confined hepatocellular carcinoma (HCC). However, predictive biomarkers of response remain to be characterised.

Method:
PRIME-HCC (NCT03682276) is an investigator-led phase Ib trial evaluating neoadjuvant nivolumab (3mg/kg, day 1, 22) and ipilimumab (1mg/kg, day 1) prior to surgery in resectable HCC. Primary endpoint is safety, assessed as treatment-related (tr) delays to surgery and adverse events (AE). Secondary endpoints included radiological and major pathological response (MPR, ≥70% tumour regression). Preplanned exploratory analyses included: (1) longitudinal circulating tumour DNA (ctDNA) profiling using a tumour-agnostic 20-gene NGS panel, (2) peripheral immunophenotyping of PBMCs by mass cytometry (CyTOF), (3) tissue single-cell and spatial transcriptomics, and (4) peripheral T-cell receptor β-chain (TCRβ) clonality analysis.

Results:
33 patients were enrolled and received at least one dose of neoadjuvant ICI. Median follow-up was 25.7 months (95%CI 21.2-30.1). Any-grade AEs occurred in 94% (n=31), with trAEs in 76% (n=25), including 9% (n=3) G3 trAEs. Surgery was completed in 30 patients (91%), including two (6%) with ICI-related delays. Radiological response was 25% (1 complete, 7 partial), and disease control 97%. MPR was observed in 33% of pathologically evaluable patients (n=27), including 22% with complete pathological response (pCR). ctDNA clearance post-surgery was associated with improved 2-year relapse-free survival (RFS, 82% vs 29%, p=0.049), as was ≥50% ctDNA reduction (p=0.015). A strong induction of peripheral PD-1+Ki-67+CD8+ T cells was observed in responding patients. The spatial analysis identified a higher baseline infiltrating pool of progenitor-exhausted T-cells (Tpex), in line with enrichment of Tpex-related transcripts (Tcf7, CD8A) in responders, and post-treatment immune exhaustion signatures in non-responders. Responders also showed more pronounced peripheral TCRβ clonal expansion (p<0.0001), associated with greater clonal migration from blood to tissue during treatment (57% vs 31% of the tissue clones, p<0.0001).

Conclusion:
Neoadjuvant nivolumab plus ipilimumab is feasible in early-stage HCC and leads to promising radiological and pathological response rates following liver resection, through profound reprogramming

of Tpex dynamics. Longitudinal ctDNA monitoring aids the detection of minimal residual disease and may be a surrogate for RFS.

OS-2
Single-cell Spatial transcriptomics of advanced HCC identifies association of CD8+ T-pure clusters with response and TREM2+-macrophage pure clusters with resistance to atezolizumab+bevacizumab

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Background and aims:
Atezolizumab plus bevacizumab (atezo+bev) is a first-line therapy for advanced hepatocellular carcinoma (aHCC) and elicits objective responses in ~30% of cases. Single-cell analyses identified $CD8^+$ T effector cells (CD8_Tex and Temra) along with $CXCL10^+$ macrophages (Macro_CXCL10) associated with treatment efficacy. Immunosuppressive $TREM2^+$ macrophages (Macro_TREM2) and $CD14^+$ monocytes (Mono_CD14) were linked to resistance. We hypothesized that the spatial organization and proximity of these immune populations within the tumor microenvironment determines response to atezo+bev.

Method:
Single-cell spatial transcriptomics (ST) profiles of 27 aHCCs (9 responders and 18 non-responders) were obtained using the Xenium Prime 5.000-gene panel (10x Genomics) customized with 100 additional genes. The distance between the cell types of interest was calculated using the frNN function ("dbscan" R package) and a radius of 300 µm. Data were normalized by tissue area and immune cell

density. Spatial clustering of $CD8^+$ T cells and Macro_TREM2 was assessed using both ST data and multiplexed immunohistochemistry staining. Clusters were defined as groups of ≥3 immune cells located within 100 µm of one another, identified through a density-based algorithm.

Results:
Single-cell ST of 27 aHCCs yielded 4.6 million cells. The distribution of CD8_Tex, CD8_Temra, and Macro_CXCL10 cells in inflamed tumors differed by treatment response: in responders, these immune populations localized inside the tumor and were closer to cancer cells (p=0.02, p=0.005, p=0.01, respectively). In addition, responder tumors were enriched in $CD8^+$-pure clusters when compared with resistant ones (81% vs 36%; p=0.02). Conversely, in resistant tumors, Macro_CXCL10 were confined at the tumor periphery. Furthermore, resistant aHCCs showed more Macro_TREM2-pure clusters and mixed Macro_TREM2-Mono_CD14 compared to responding tumors (43% vs. 5%; p=0.04; 18% vs. 5%; p=0.07). At the multiplex level, we confirmed an increased abundance of Macro_TREM2-pure clusters in resistant tumors (26% vs. 0% in responders, p=0.02) and a higher frequency of mixed Macro_TREM2-$CD8^+$ clusters (38% vs. 18% in responders, p=0.03).

Conclusion:
Our single cell spatial transcriptomics analysis in aHCC uncovers a distinct immune architecture in responders to atezo+bev with pure clusters of $CD8^+$ T cells, and resistant tumors with peripheral localization of $CXCL10^+$ macrophages and pure clusters of $TREM2^+$ myeloid cells.

OS-3
Four-year survival and safety analysis from the Phase 3 TOPAZ-1 study of durvalumab plus chemotherapy in biliary tract cancer

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Background and aims:
In the primary analysis of the TOPAZ-1 study, durvalumab (D) + gemcitabine and cisplatin (GC) significantly improved overall survival (OS) vs placebo (PBO) + GC, with a manageable safety profile in participants (pts) with advanced biliary tract cancer (aBTC). This final *post hoc* analysis aimed to evaluate 4-year OS and safety.

Method:
Pts with aBTC received D or PBO + GC every 3 weeks followed by D or PBO monotherapy every 4 weeks. OS, exposure, adverse events (AEs) resulting in discontinuation, and serious AEs (SAEs) were assessed ~ 48 months (mo) after the last pt was randomised (data cut-off: 28 Feb 2025).

Results:
Overall, 685 pts were randomised to D + GC (n = 341) or PBO + GC (n = 344). The median (range) follow-up in censored pts was 56.9 (1.7–67.2) mo for pts receiving D + GC and 50.7 (0.9–62.6) mo for pts receiving PBO + GC. The median OS (mOS; 95% CI) was 13.0 (11.6–14.1) mo for D + GC and 11.4 (10.1–12.5) mo for PBO + GC (HR, 0.75; 95% CI, 0.6–0.9). The 48-mo OS rate was 11.8% for D + GC vs 4.3% for PBO + GC. Of the total pts in both groups, 380 (55.5%) received subsequent anti-cancer therapy, of which cytotoxic chemotherapy was the most common (51.8%), followed by other treatments (9.2%), targeted therapy (8.5%) and immunotherapy (6.0%). Overall, 8.1% of pts who had received PBO + GC received subsequent immunotherapy, compared with 3.8% of pts who had received D + GC. Median exposure to D or PBO was 7.3 mo for D + GC vs 5.8 mo for PBO + GC. Mean exposure to D was 9.4 mo for D + GC compared with 9.0 mo for D + GC in the 3-year OS analysis. Overall, the rate of SAEs possibly related to treatment was similar between arms and the safety profile was consistent with prior analyses. Since the 3-year OS analysis, no additional pts had AEs leading to discontinuation; 3 pts in the D + GC arm had additional SAEs unrelated to treatment with no change in the PBO + GC arm.

Conclusion:
This is the first randomised Phase 3 study to report 4-year OS in aBTC using a combined immunotherapy and chemotherapy approach. After 4 years of follow-up, D + GC continued to demonstrate consistent clinically meaningful long-term survival benefit. The safety profile remains manageable with no new safety signals identified compared with the prior analyses and no new SAEs possibly related to treatment despite prolonged exposure to D in the D + GC arm. This further supports standard of care status for D + GC in pts with aBTC.

OS-4-YI
Transjugular intrahepatic portosystemic shunt promotes hepatocellular carcinoma growth in metabolic dysfunction associated liver disease

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Background and aims:
Transjugular intrahepatic portosystemic shunt (TIPS) reduces complications of portal hypertension, but its impact on hepatocellular carcinoma (HCC) remains debated, especially in metabolic dysfunction-associated steatotic liver disease (MASLD). We aimed to determine whether TIPS alters HCC growth and transcriptional programs.

Method:
Bulk RNA sequencing was performed on HCC samples from 34 patients with or without TIPS. Diethylnitrosamine (DEN)-induced HCC mouse models under normal diet (ND) or high-fat diet (HFD, MASLD model) were used to study tumor growth and molecular profiles after surgical portosystemic shunt. Findings were validated using the Scientific Registry of Transplant Recipients (SRTR) in propensity score-matched MASH patients (n=792).

Results:
Human transcriptomes showed enrichment of immune pathways after TIPS, with five upregulated genes including FABP4, GCK and FOSB, associated with better survival in an independent dataset. ND-shunted mice had no change in HCC growth, whereas MASLD mice displayed accelerated tumor progression (1.14 vs 0.22 mm^3/week, $p<0.001$) with activation of metabolic and proliferative programs. In SRTR MASH patients, TIPS was linked to faster tumor growth (0.26 vs -0.42 cm^3/month in no TIPS patients, $p=0.003$), consistent with experimental mouse findings.

Conclusion:
These findings demonstrate that TIPS leads to diverging effects on HCC depending on the metabolic context: immunostimulatory in non-MASLD and tumor-promoting in MASLD. These results warrant further validation but suggest that the use of TIPS in MASLD-related HCC patients should be monitored carefully.

OS-5-YI

Efficacy of immune checkpoint inhibitors (ICIs) in patients with HIV-associated unresectable HCC (uHCC): a propensity-score matched analyses from two international consortia

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Background and aims:
People living with HIV(PWH) have commonly been excluded from clinical trials, therefore, data about the safety and efficacy of immune-checkpoint inhibitors(ICI) in PWH affected by unresectable HCC (uHCC) are lacking.

Method:
Using data from 2 international consortia (CATCH-IT and AB-Real), we selected a cohort of PWH and people without HIV (PWOH) affected by uHCC treated with ICIs and compared their outcomes. Primary endpoints were overall (OS) and progression-free survival (PFS). Propensity score matching (PSM) was performed for age, sex, aetiology of liver disease, Child-Pugh class (CP-C), ECOG-PS, BCLC stage, alpha-fetoprotein (AFP), portal vein tumour thrombosis, extrahepatic spread, treatment line and regimen. Targeted RNA sequencing using nCounter Nanostring platform was performed on matched pre-treatment biopsies (N=8 PWH;9 PWOH).

Results:
We accrued 52 PWH and 996 PWOH, 63.5% and 72.4% were treated in first line, with either combination treatment (34.7%vs55%) or antiPD-1 monotherapy. Median age at ICI start was 62 (IQR 55-67) and 66 (IQR 59-73) years; viral hepatitis was more prevalent in PWH (92.2%vs52.9%); most patients had

BCLC-C HCC (82.7% vs 76.2%). In PWH, HIV viraemia was undetectable in 45 patients and all were established on anti-retrovirals. Following PSM, 50 PWH and 141 PWOH remained. Median OS was 7.1 months, (95%CI: 4.1-NR) in PWH and 12 months (95%CI: 7.5-19.5) in PWOH (HR: 0.98 95%CI: 0.64-1.51; p=0.93). Median PFS was 2.8 months (95%CI: 2.1-3.5) vs 4.0 months (95%CI: 3.0-7.1), respectively (HR:1.06 95%CI: 0.72-1.54, p=0.76). All grade immune-related adverse events (irAEs) were less frequent in PWH (25% vs 45.4%, p=0.006), with similar incidence of grade≥3 irAEs (13.5%vs14.3%). No differences were observed in the incidence of bleeding (7.7% vs 7.2%). Differential gene expression analysis of pre-treatment samples revealed no significant differences between the two cohorts. However, non-responders to immunotherapy had enrichment of genes associated with innate immunity, as *CD68*, *C1QA, LYZ2*, and *PLA2G2A*. A score based on 28 immune-related transcripts allowed identification of monocytes (p=0.016) and macrophages (p=0.002) in non-responders independent of HIV status.

Conclusion:
This study provides practice-informing evidence to support the use of ICIs in PWH and uHCC and encourages the inclusion of patients with well-controlled HIV in prospective clinical trials.

The study was funded by Conquer Cancer Foundation Global Oncology Young Investigator Award to Dr. Fulgenzi

OS-6
Factors associated with liver imaging uptake and hepatocellular carcinoma incidence in the UK multicentre cirrhosis Pearl (Prospective Cohort for Early Detection of Liver Cancer) cohort

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Background and aims:
Hepatocellular carcinoma (HCC) is the fastest-rising cause of cancer death globally, with around 6600 new cases per year in the UK (2017-2019). Approximately 90% of HCC arises in liver cirrhosis, yet early detection remains suboptimal, with over 70% diagnosed at advanced stage. The Pearl study, part of the CRUK-funded DeLIVER programme, is a multicentre prospective cohort aiming to improve early HCC detection by following 3,000 patients with cirrhosis from 44 UK liver clinics. This analysis explores factors associated with liver imaging uptake in the year prior to enrolment and HCC incidence.

Method:
We analysed data from the Pearl cohort from September 2025, 43 months after study inception. A total of 2,000 patients with cirrhosis were included. Logistic regression was used to identify factors associated with having ≥1 liver imaging scan (ultrasound, CT or MRI) in the year prior to enrolment. Cox proportional hazards regression was used to assess associations with HCC incidence. Analysis was undertaken in R version 4.4.2.

Results:
Among 2,000 participants (63.4% male, mean age 61.6), 79.5% had ≥1 liver imaging scan in the past 12 months, and there are 65 HCC diagnoses. In multivariable logistic regression, imaging uptake was associated with increasing age (odds ratio or OR per 10 years: 1.19, $p = 0.005$), site type, with lower uptake in liver units (OR: 0.43, $p < 0.001$) and non-specialist units (OR: 0.23, $p < 0.001$) compared to transplant centres, and history of hepatic decompensation (OR: 1.41, $p = 0.036$). Gender and liver disease aetiology were not independently associated with imaging uptake.

HCC incidence was 1.56 per 100 person-years (95% confidence interval 1.21-1.99). In univariable Cox regression, HCC incidence was associated with male sex (hazard ratio or HR: 2.52, $p = 0.003$), older age (HR per 10 years: 1.49, $p = 0.0038$), aMAP score (HR: 1.11 per unit, $p < 0.001$), and haemochromatosis (HR: 3.85, $p = 0.007$). In multivariable analysis (adjusted for age, gender and aetiology), male gender (HR: 2.52, $p = 0.0034$) and age (HR: 1.49, $p = 0.0038$) remained significantly associated with HCC.

Conclusion:
Despite guidelines recommending 6-monthly liver imaging in cirrhosis, uptake varies significantly by age, clinical site, and decompensation history. Gender and age are strongly associated with HCC incidence. These findings highlight ongoing gaps in surveillance delivery and reinforce the need for risk-stratified screening strategies to improve HCC early detection in cirrhosis populations.

OS-7-YI

Hepatectomy-induced immune suppression limits the efficacy of adjuvant programmed cell death 1 blockade but not neoadjuvant in hepatocellular carcinoma

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Background and aims:
Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality, with high recurrence rates after curative hepatectomy. While immune checkpoint inhibitors (ICI) have improved the management of advanced HCC, their integration into the perioperative setting is still undefined. This study investigated how hepatectomy shapes the tumor microenvironment (TME) and evaluated the efficacy of neoadjuvant versus adjuvant programmed cell death 1 (PD-1) blockade.

Method:
An orthotopic murine HCC model was established by injecting luciferase-expressing RIL-175 cells into the liver. Mice underwent either non-curative or curative partial hepatectomy and were randomized to receive anti-PD-1 therapy in neoadjuvant or adjuvant settings. Tumor growth was followed by bioluminescence imaging, and the TME was characterized using flow cytometry, RNA sequencing, and immunohistochemistry. Cytokine profiling was performed on postoperative serum. In a separate experiment, curative hepatectomy was performed to evaluate recurrence and survival.

Results:
Anti-PD-1 significantly reduced tumor growth in non-surgical models, both intrahepatic and subcutaneous. However, its efficacy was lost when administered post-hepatectomy, correlating with a loss of effector CD103+CD8+ T cells, increased expression of exhaustion markers (TIM-3, LAG-3), and accumulation of immunosuppressive myeloid subsets (MDSC, pDC). Cytokine profiling of postoperative serum revealed an early innate cytokine surge (IL-6, CXCL1/2) and a persistent wound-healing signature (CCL2, VEGF-A). Adjusting therapy by depleting myeloid-derived suppressor cells or delaying anti-PD-1 administration to avoid the immunosuppressive window partially restored activity. In contrast, neoadjuvant anti-PD-1 preserved cytotoxic T-cell function, promoted immune infiltration, and induced upregulation of key activation markers (TBX21, GZMA, CXCR6, CD69), with fewer vascular/lymphatic invasions compared to adjuvant treatment. Following curative hepatectomy, neoadjuvant but not adjuvant therapy, significantly reduced recurrence and prolonged survival.

Conclusion:
Hepatectomy induces a temporary immunosuppressive environment that disrupts anti-tumor immunity and limits the efficacy of adjuvant ICI. Neoadjuvant immunotherapy preserves T-cell function, reduces recurrence, and prolongs survival, supporting neoadjuvant PD-1 as a superior perioperative strategy in HCC.

OS-8-YI
Histomorphologic characteristics of response to neoadjuvant immune checkpoint inhibitor therapy in hepatocellular carcinoma

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Background and aims:
Neoadjuvant immune checkpoint inhibitor (nICI) therapy is an emerging treatment option in early-stage hepatocellular carcinoma (HCC). Although the extent of post-treatment tumour regression defines major pathologic response (MPR) and predicts treatment benefit in various solid tumours, comprehensive histomorphologic evaluation of the underlying response features remains lacking for HCC. Hence, our study aims to characterise the histomorphologic features associated with response to nICI therapy in HCC.

Method:
We analysed 293 H&E-stained liver resection slides from 86 patients from the NeoHCC consortium, from the UK (n = 28), USA (n = 42), and Taiwan (n = 16). The percentage of tumour bed surface area occupied by residual viable tumour defined pathologic response, with an MPR threshold of ≥ 90% tumour regression. Tumour-infiltrating lymphocytes (TILs) were scored semi-quantitatively from absent/scattered (low) to moderate/heavy (high). We assessed the presence of histologic features informed by the pan-cancer response criteria. We used Fisher's exact test to identify MPR-enriched features and employed Kaplan-Meier and Cox regression analyses to evaluate associations with recurrence-free survival (RFS).

Results:
Patients were treated from 08/2017 to 11/2023 with nICI monotherapy (33%) or combinations (67%) before undergoing liver resection. Most were male (74%), had viral HCC aetiology (62%) with BCLC stage 0-A (64%); 18% had portal vein thrombosis. All patients had an ECOG performance status of 0-1. The radiological objective response rate (RECIST 1.1) was 25% (n = 21). In 85 patients eligible for analysis (median follow-up 23.6 months, 95%CI: 19.6-34.1), MPR correlated with a significantly prolonged RFS (HR = 0.10, 95%CI: 0.01-0.72, p = 0.023). One recurrence occurred in 20 MPR patients versus 24 of 65 non-MPR patients (mRFS NR in both, 95%CI: NR-NR vs 19.2-NR, log-rank p = 0.005). Histomorphological features enriched in major responders included high TIL scores (n = 15, 75%, p < 0.001), presence of haemosiderin (n=7, 35%, p = 0.016), dense plasma cells (n = 4, 20%, p = 0.024), and cholesterol clefts (n = 3, 15%, p = 0.038). The MPR-enriched features did not provide independent prognostic value for RFS.

Conclusion:
This is the first study to comprehensively describe the histopathologic features associated with response to nICI in HCC. While MPR robustly captures nICI-driven RFS benefit, histomorphologic changes associated with MPR may give further mechanistic insights into nICIs.

OS-9
PROACTIF: Final results from the largest prospective real-world study of 1196 primary liver cancer patients treated with yttrium-90 glass transarterial radioembolization

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Background and aims:
This study evaluated the effectiveness, quality-of-life, safety, and dosimetry of yttrium-90 (Y90) glass microspheres for the treatment of primary and secondary liver cancer in a real-world clinical setting. Herein, we present the data for patients with hepatocellular carcinoma [HCC] and intrahepatic cholangiocarcinoma [iCCA].

Method:
All patients treated with Y90 glass microspheres (TheraSphere™) in 34 French institutions between 2019 and 2024 who agreed to data collection were included. Duration of follow-up and overall survival (OS) were assessed by reverse Kaplan-Meier (KM) and KM analysis, respectively. Toxicity was assessed using CTCAE v5. BCLC was programmatically derived.

Results:
In total, 1196 patients with primary liver cancer (PLC) (989 HCC; 207 iCCA) were included. Of the HCC patients, 35.3% had portal vein thrombosis; 13.3%, 18.9%, 57.9%, and 5.8% were BCLC stage A, B, C, D, respectively. Among iCCA patients, 56.5% were ECOG 0; 31.9% had associated liver fibrosis/cirrhosis. At least one prior treatment was reported in 39% of patients (systemic, n=194; locoregional [LRT], n=289; surgery, n=72). Median OS (mOS) was 21.8 months (M) for HCC and 21.9M for iCCA. mOS was 21.3M and 22.1M for HCC patients with and without prior systemic treatment, respectively. mOS for iCCA patients treated with first-line TARE was 23.3M compared with 11.4M as a second-line treatment. 54% of PLC patients had subsequent treatment; patients who had post-Y90 surgery (12%) had the greatest OS benefit. In HCC, mOS was 48.6M with subsequent surgery (n=112), 23.3M with subsequent LRT or systemic treatment (n=424), and 14.8M with no further treatment (n=396). In iCCA, mOS was not reached in patients with subsequent surgery (n=27), 21.3M for patients with subsequent LRT or systemic treatment (n=90), and 17.4M for patients without subsequent treatment (n=76). Among all patients, 93 experienced adverse events (AEs; n=134), 88 had serious AEs (n=114), and 45 patients had related/possibly related serious treatment-emergent AEs (3.8%).

Conclusion:
Results from this large prospective real-world study using tailored Y90 treatment highlight its critical role as an integral component in the continuum of care for patients with PLC. There was meaningful survival, and an acceptable adverse event profile in both indications. Importantly, Y90 followed by surgery resulted in survival outcomes rarely observed in this population of patients typically not eligible for surgery.

OS-10-YI
Clinical and molecular characterisation of primary refractoriness to atezolizumab plus bevacizumab in patients with hepatocellular carcinoma

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Background and aims:
Primary refractoriness (PRef) represents a major clinical unmet need in patients (pts) with hepatocellular carcinoma (HCC) treated with atezolizumab plus bevacizumab (A+B). However, mechanisms underlying PRef remain poorly understood.

Method:
To characterise PRef, we analysed a multinational cohort of 1317 pts treated with frontline A+B (AB-real) and validated findings in 654 trial participants to IMbrave150 and GO30140. PRef was defined by SITC criteria as progressive or stable disease for <6 months as best response. Kaplan-Meier and Cox regression analyses assessed the prognostic impact of PRef on overall survival (OS) against non-progressors (NP). Multi-platform profiling of pre-treatment tumour tissue included RNA sequencing (RNAseq), imaging mass cytometry (IMC), and machine-learning quantification of tumour-infiltrating lymphocytes (TILs).

Results:
Among 677 AB-real and 378 trial pts evaluable by SITC criteria, median OS was significantly worse in PRef vs. NP (AB-real: 7.3 vs. 31.5 months, HR 3.7, 95%CI 2.8–8.5, p<0.001; trials cohort: 10.8 vs. NR, HR 4.6, 95%CI 3.3–6.3, p<0.001). Multivariate models confirmed PRef as an independent predictor of OS across cohorts (AB-real: HR 4.0, 95%CI 2.8–5.5; trial cohort: HR 4.9, 95%CI 3.6–6.7). PRef pts had higher baseline inflammation (Neutrophil-to-lymphocyte ratio, NLR ≥3 in 63% and 65% vs 40% and 35% in AB-real and trials, both p<0.001) and distinct TME features by IMC (n=43) including enriched T_{reg}, $CD163^{low}$ macrophages and higher T_{reg}/T_{eff} ratio, with no difference in overall TIL counts. RNAseq analysis on trial samples (n=229) demonstrated lower intrinsic immunogenicity in PRef pts, hallmarked by repression of T_{eff} (p=0.001), IFN-g (p=0.0005) and T_{eff} signature/myeloid-derived-suppressor cell (MDSC, p=0.001) gene signatures, each independently associated with reduced OS (T_{eff} HR 2.38,

95%CI 1.21–4.6, p=0.01, IFN-g: HR 3.32, 95%CI 1.64-6.71, p<0.001, T_{eff}/MDSC: HR 2.41, 95%CI 1.21–4.8, p=0.01). In contrast, among pts treated with sorafenib in the IMbrave150, immune-related signatures were not enriched among long-term responders (>6 months), underscoring the specificity of these signatures as predictors of immunotherapy responsiveness.

Conclusion:
PRef to A+B identifies a biologically distinct, poorly immunogenic and systemically inflamed HCC subtype associated with adverse outcomes. Targeting immunosuppressive pathways within the TME may enhance benefit from A+B in this unfavourable population.

OS-11-YI
Clinical predictors and molecular architecture of tertiary lymphoid structures in cholangiocarcinoma.

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Background and aims:
Intrahepatic cholangiocarcinoma (iCCA) is an aggressive malignancy with immunologically cold features and poor prognosis. Tertiary lymphoid structures (TLSs) are ectopic immune aggregates resembling lymph nodes that can support anti-tumor immunity. We recently reported that mature TLSs correlate with improved survival in iCCA (Milardi G, Gut 2025). Here, we aimed to identify clinicopathological predictors and characterize the molecular composition of TLSs in iCCA.

Method:
Electronic medical records and surgical samples from patients with iCCA treated at Humanitas Research Hospital between 2011 and 2022 were analyzed. TLSs were identified by immunohistochemical staining for CD3 and CD20 in tumor and peri-tumor regions, with maturation being defined by the presence of germinal center-like organization (B-cell cores surrounded by T cells). Spatial transcriptomic profiling of representative intra-tumor and peri-tumor TLSs and matched tumor-negative lymph nodes was performed using the GeoMx Digital Spatial Profiling platform (Whole Transcriptome Atlas). Associations between TLS features and clinicopathological variables were tested using Fisher's exact or Chi-square tests (two-sided $p<0.05$). Transcriptomic data were analyzed using R packages (GeomxTools, SpatialDeconv, CellphoneDB).

Results:
Among 103 patients, 51 (49.5%) presented TLSs (51% intra-tumoral, 49% peri-tumoral), of which 39 (77%) were mature. Median age was 70 years (range 37-84), 47% were male, and 45% had stage I disease. TLS presence correlated with lower pathological T stages (T1-2 vs T3-4: 53% vs 23%, p=0.04), presence of metabolic comorbidities (57% vs 31%, p=0.02), and liver steatosis (63% vs 39%, p=0.01). Mature TLSs were more frequently intra-tumoral (85% vs 68%) and significantly associated with earlier TNM stages (I-II vs III-IV: 45% vs 22%, p=0.02). Spatial transcriptomics (n=3 patients, 13 ROIs) revealed enrichment of B memory and CD4 memory T cells in TLSs versus lymph nodes, with intra-tumoral TLSs showing the highest number of B-T cell interactions.

Conclusion:
TLSs are relatively frequent in iCCA, with mature aggregates being observed in most cases, particularly in intra-tumoral areas. Mature, intra-tumoral TLSs are associated with earlier disease stages and are enriched in "highly interactive" B and T memory populations, suggesting they may serve as preferential sites of local immune priming in iCCA.

POSTER ABSTRACT PRESENTATIONS

Basic Science

PT-1-YI

Cancer-associated fibroblasts in hepatocellular carcinoma tumor microenvironment and prediction of resistance to atezolizumab + bevacizumab treatment

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Background and aims:
The combination of atezolizumab+bevacizumab (atezo+bev) is a first-line therapy for advanced-stage hepatocellular carcinoma (HCC). Cancer-associated fibroblasts (CAF) support survival of cancer cells by promoting immunosuppression. This study aims to characterize CAF subtypes in HCC and evaluate their impact on immunotherapy (IO) responses.

Method:
Seven single-cell RNA sequencing (scRNA-seq) HCC cohorts (197 tumors; 446,075 cells) were integrated to delineate stromal compartments and identify CAF subtypes. CAF signatures were derived and projected onto bulk RNA-seq from early and late HCC cohorts (n=578) using the deconvolution algorithm BayesPrism. CAF signatures were integrated into the previously established molecular and immunological classifications of HCC. Differential expression of bulk RNA-seq data of HCCs treated with atezo+bev (n=386) and LASSO regression yielded a 22-gene CAF signature of response to treatment (AB-CAF). Its added value was benchmarked against published treatment-response signatures and was also tested in sorafenib-treated patients from the IMbrave150 trial (n=58). Associations with outcome were also evaluated.

Results:
Six distinct transcriptional CAF identities were unveiled in HCC. Overall, they corresponded to 5-15% of the tumor lesions in early and advanced HCC, respectively. “iMyo/POSTN”, mainly involved in extracellular matrix remodelling, was the most prevalent CAF subtype across disease stages (63% in early, 90% in advanced, among all CAF cells). Resistance to atezo+bev was associated with a CAF-derived gene signature, which proved to be specific vs sorafenib (p of interaction = 0.007). This AB-CAF signature differed from previously reported IO/atezo+bev response signatures due to its stromal identity and retained independent predictive value in multivariate analysis (OR 4.26, 95% CI 2.45-7.58; p < 0.001).

Conclusion:
CAF account for 5-15% of the HCC tumor lesions, with iMyo/POSTN CAFs representing the most prevalent subtype across disease stages. AB-CAF gene signature independently predicted resistance to atezo+bev in advanced HCC.

PT-2-YI

The Hypoxic niche shapes cancer-associated fibroblast heterogeneity in hepatocellular carcinoma and uncovers a therapeutic vulnerability

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Background and aims:
Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide. A major clinical challenge in treating advanced, unresectable HCC is the limited efficacy of current immunotherapies. The combination of Atezolizumab (anti–PD-L1) and Bevacizumab (anti–VEGF) (AtezoBev) exhibits improved survival compared to previous standard-of-care treatments; however over 70% of patients display refractory responses, with minimal benefit or disease progression within six months. Bulk RNA sequencing and imaging mass cytometry analyses in responsive and refractory tumours revealed enrichment of multiple cancer-associated fibroblast (CAF) populations and increased hypoxia signalling in AtezoBev-resistant cases. This study therefore aimed to characterise CAF heterogeneity in HCC and evaluate the potential of CAF-targeted therapies to enhance immunotherapy responsiveness.

Method:
Using a machine learning-based framework, protein expression profiles were comprehensively mapped across CAF subsets in an orthotopic murine HCC model. An optimised antibody panel was developed to delineate CAF subpopulations alongside pimonidazole hydrochloride for hypoxia detection. To interrogate the role of hypoxic response in CAFs, a conditional knockout of HIF1α in CAF-lineage cells was established. Pharmacological interventions using SLC-0111 (carbonic anhydrase IX inhibitor) or an ALK5 inhibitor (TGFβ receptor I blockade) were applied at mid-stage tumour development.

Results:
CAF heterogeneity was markedly increased in hypoxic tumour regions, implicating hypoxia as a key driver of CAF diversification, particularly in subsets associated with immunosuppression (apCAFs) and AtezoBev resistance (vCAFs). Conditional deletion of HIF1α in CD140β$^+$ fibroblasts significantly reduced tumour burden and depleted both vCAF and apCAF populations. *In vivo* SLC-0111 treatment similarly diminished these subpopulations while expanding matrix-producing CAFs (mCAFs) and enhancing CD8$^+$ T-cell infiltration. ALK5 inhibition reduced intratumoral collagen, increased CD8$^+$ T-cell recruitment, and shifted CAF composition toward a more quiescent phenotype, suggesting suppression of CAF activation through TGFβ pathway inhibition.

Conclusion:
Collectively, these findings identify hypoxia-driven CAF plasticity as a critical mechanism of immunotherapy resistance in HCC and support a therapeutic framework in which CAF-targeted interventions precede immunotherapy to reprogram the tumour microenvironment for improved clinical outcomes.

PT-3
Inflammation-driven IL-1β–NOTCH signalling promotes pre-neoplastic transitions in biliary epithelium

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Background and aims:
Chronic inflammation markedly increases cancer risk, yet how inflammatory cues interact with pre-existing somatic mutations to initiate neoplasia remains unclear. In cholangiocarcinoma (CCA), patients with inflammatory disorders such as primary sclerosing cholangitis (PSC) exhibit the highest risk, but the earliest cellular and molecular events that transform benign biliary epithelial cells (BECs) are undefined. We sought to determine how inflammation reprogrammes mutant BECs to promote neoplastic initiation and to identify tractable targets that prevent this transition.

Method:
Using a biliary-specific *Trp53;Pten*-loss mouse model of CCA, we combined single-cell RNA-sequencing (>21,000 cells), spatial immunophenotyping, and organoid models to define inflammation-dependent epithelial states. Data were integrated with human PSC, primary biliary cholangitis (PBC), and BilIN scRNA-seq and histopathology datasets to determine conservation across species. Pharmacological and genetic perturbation of COX2 and NOTCH pathways tested causality *in vivo*.

Results:
Loss of *Trp53* and *Pten* sensitised large-duct BECs to inflammatory signalling, generating a $COX2^+$ ($Ccl2^+$/$Ccl7^+$/$Mmp7^+$) pre-neoplastic state associated with IL-$1\beta^+$ macrophage recruitment. These epithelial states were reproduced in human BilIN and in a PSC subset but not in PBC or healthy bile ducts. Although COX2 inhibition (aspirin, celecoxib) failed to suppress tumour initiation, inflammation cessation or blockade of NOTCH signalling—via *Rbpjκ* deletion or the γ-secretase inhibitor Crenigacestat—prevented BilIN formation. Conversely, ectopic NOTCH activation was sufficient to drive neoplasia without inflammation.

Conclusion:
Inflammation permits tumour initiation by re-wiring IL-1β–NOTCH signalling in mutant biliary epithelium, establishing an oncofoetal state that drives early neoplasia. Targeting developmental reactivation through Notch inhibition offers a rational prophylactic strategy for patients with chronic biliary inflammation at high risk of cholangiocarcinoma.

PT-4-YI

Metabolic rewiring by increased mitochondrial respiration drives immune evasion and brain metastasis in hepatocellular carcinoma

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Background and aims:
Recent evidence suggests a shift towards a more mitochondria-based metabolism in advanced hepatocellular carcinoma and metastatic cancer cells. In this context, we focused on methylation control J protein, an endogenous negative regulator of mitochondrial complex I, the absence of which enhances mitochondrial respiration and reduces oxidative stress. We investigated the role of MCJ in different stages of HCC to determine whether oxidative tumors exhibit increased malignancy, how this metabolic phenotype modulates the immune response and whether it contributes to metastatic progression.

Method:
MCJ expression was analyzed in three publicly available RNA-seq datasets. Two mouse models of HCC were used. First, wild-type (WT) and whole-body $Mcj^{-/-}$ mice were treated with diethylnitrosamine (DEN) for 5, 8 or 12 months. Second, C57BL/6 mice were injected with a MYC;sgp53 plasmid combination, and *Mcj* was specifically knocked down in hepatocytes. In both models, tumor progression, liver metabolism, mitochondrial activity and tumor-infiltrating immune cells were investigated.

Results:
Analysis of Gene Expression Omnibus (GEO) data revealed that MCJ is downregulated in HCC compared to healthy liver. In TCGA, MCJ expression was reduced in stage IV HCC patients. In an independent cohort comparing aggressive and non-aggressive HCC patients, MCJ was specifically downregulated in tumor tissue from aggressive cases characterized by increased TGF-β signaling and metastatic features. *In vivo*, MCJ deficiency increased DEN-induced tumorigenesis and mortality, with brain metastases observed at 12 months. $Mcj^{-/-}$ tumors exhibited enhanced mitochondrial respiration, increased ATP, NAD^+ and NADPH levels, and decreased infiltration of effector T cells, along with lower serum levels of IFNγ and TNF. Proteomic analysis revealed upregulation of lipid metabolism and antioxidant signaling pathways. Hepatic M*cj silencing* in the MYC;sgp53 model also promoted tumorigenesis and brain metastasis formation. Finally, we established an $Mcj^{-/-}$ HCC cell line from DEN-treated mice whose proliferation was selectively reduced by inhibition of fatty acid oxidation, but not by inhibition of glycolysis or glutaminolysis.

Conclusion:
Metabolic rewiring and metastasis are closely linked in HCC. The observed downregulation of MCJ in advanced and aggressive HCC, together with our in vivo findings, highlights MCJ as a potential marker of metastatic risk and a candidate for guiding metabolic biomarker discovery in advanced HCC.

PT-5
An Artificial Intelligence-driven proteomic model to predict treatment response for systemic therapies in advanced hepatocellular carcinoma

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Background and aims:
The therapeutic landscape for advanced hepatocellular carcinoma (HCC) has expanded to include multiple systemic therapies with distinct mechanisms of action, such as different classes of immunotherapies and tyrosine kinase inhibitors (TKIs). This progress creates a critical clinical challenge: the absence of predictive tools to guide the selection of the optimal treatment for each patient. Our aim was to develop a predictive model based on proteomic profiling and machine learning to generate treatment-specific response scores, enabling personalized therapeutic guidance.

Method:
We profiled a cohort of 100 formalin-fixed, paraffin-embedded (FFPE) diagnostic biopsies from advanced HCC patients using high-resolution mass spectrometry. For each patient, a tumor-specific proteomic profile was generated by comparing protein abundances between matched tumoral (T) and adjacent non-tumoral (NT) tissues. Patients were stratified into 'responders' or 'progressors' based on clinical outcomes for several treatments. These curated data were used to train a machine learning model designed to predict treatment-specific response scores.

Results:
We successfully developed a predictive model capable of generating response scores for multiple systemic therapies, including two distinct classes of immunotherapy combinations and TKIs. The model is built upon unique proteomic signatures for each treatment class, demonstrating a high degree of specificity. Crucially, analysis of these signatures revealed distinct and non-overlapping biological pathways associated with response to each therapy. This was observed even between the two classes of immunotherapy combinations, suggesting different underlying mechanisms of action and resistance. The resulting predictive scores showed a strong correlation with observed clinical responses, indicating the model's potential to accurately stratify patients.

Conclusion:
This study establishes a novel, AI-driven proteomic model that generates predictive response scores for the main systemic treatments in advanced HCC. By providing a biological rationale for treatment selection, this tool has the potential to guide oncologists, improve patient management, and advance personalized medicine in this challenging disease.

PT-5-YI

In vitro identification of immunogenic tumoral antigens in advanced hepatocellular carcinoma reveals new opportunities for therapeutic applications

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Background and aims:
The antigenic landscape underlying the antitumor immune response remains poorly characterized. Existing methods for antigen identification or prediction are limited in accuracy, often restricted to exonic mutations, and frequently lack experimental validation of immunogenicity. Systematic identification of tumoral antigens is critical for the development of novel immunotherapy strategies in advanced HCC (aHCC). We aimed to map the antigenic repertoire in aHCC using a novel unbiased, transcriptome-wide approach which includes functional validation.

Method:
Pre-treatment and on-treatment tumor biopsies were obtained from a patient with aHCC who achieved a complete pathological response following treatment with durvalumab plus tremelimumab. By applying single-cell RNA and T-cell receptor (TCR) sequencing, we identified the TCRs of the 12 most expanded $CD8^+$ T-cell clones in each tissue sample. After excluding duplicate TCRs between timepoints, 19 patient-specific, potentially tumor-antigen directed TCRs were selected. Each TCR was transfected in a T cell line and cocultured with an HLA matched antigen-presenting cell (APC) line expressing the patient-specific tumor transcriptome library. Clusters of APCs with activated T cells were isolated, expanded and the antigenic sequence incorporated in the APC was retrieved by sanger sequencing.

Results:
We identified a tumoral antigenic sequence for 10 out of 19 TCRs analyzed. Only 2 of the antigens were based on a mutation, whereas the others represented the reactivation of a novel cancer-testis antigen, overexpressed genes and alternative open reading frames. Expression of several of the detected antigens identified in this patient was also detected in tumors from other HCC patients and across other tumor types within the TCGA dataset, indicating the presence of shared tumor antigens between cancer patients. Remarkably, 4 different TCRs were found to recognize the same antigen. For 9 out of 10 TCRs with an identified tumoral antigen, the corresponding T cell clonotype was detected in the tumor biopsy prior to immune checkpoint inhibition (ICI), indicating an ongoing immune response against these antigens before ICI.

Conclusion:
Using a novel antigen detection platform, we confirmed that diverse genomic alterations, ranging from exonic mutations to events in the dark genome, can give rise to immunogenic antigens capable of eliciting T-cell responses. The identification of shared tumoral antigens opens new opportunities for therapeutic applications.

PT-6
α-Ketoglutarate–driven immune escape in hypoxic Metabolic Dysfunction-Associated Steatotic Liver Disease - related Hepatocellular Carcinoma: amino acid metabolism at the crossroads

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Background and aims:
MASLD-related hepatocellular carcinoma (HCC) is an emerging global health concern, driven by the rising prevalence of obesity, type 2 diabetes, and metabolic syndrome. As metabolic dysfunction-associated steatotic liver disease (MASLD) progresses to HCC, profound alterations in the tumor microenvironment (TME) contribute to tumor aggressiveness and immune evasion. Hypoxia is a defining feature of the TME and drives metabolic reprogramming, including increased utilization of branched-chain amino acids (BCAA) and glutamine, which fuel tumor growth and generate oncometabolites that potentially reshape the tumor immune landscape. This study explores how hypoxia, through BCAA and glutamine catabolism remodelling, affect pro-tumoral macrophage polarization and immune evasion.

Method:
This was investigated in: a) cohorts of MASLD/MASH-HCC patients; b) murine models for disease progression from MASLD (CDAA diet) to MASH-related HCC (DEN/CDAA protocol) with hepatocytes deletion for HIF-2α (HIF-2α$^{-/-}$); c) in vitro experiments on HepG2 cells and macrophages THP-1 cells.

Results:
Our findings indicate that hypoxic conditions upregulate the expression of the BCAA transporter LAT1 and the glutamine-metabolizing enzyme glutaminase 1 (GLS1) in both *in vitro* and *in vivo* models and patient-derived MASH-HCC tissues, with their expression levels being positively associated with hypoxia-inducible factor 2α (HIF-2α). In the MASLD-HCC experimental model, elevated serum BCAA levels and increased hepatic expression of catabolic enzymes (BCAT1/2, GLS1/2, GLUD) were observed, while hepatocyte-specific HIF-2α knockout markedly reduce their levels. Activation of these pathways, alongside altered regulation of TCA-cycle enzymes, likely drives α-ketoglutarate (α-KG) accumulation, promoting M2-like polarization of macrophages and contributing to immune evasion within the TME.

Conclusion:
In summary, hypoxia-induced reprogramming of BCAA and glutamine metabolism in MASLD-related HCC contributes to immune evasion via oncometabolite-driven mechanisms. Targeting these metabolic nodes may offer new therapeutic strategies to restore anti-tumor immunity in this increasingly prevalent cancer subtype.

PT-6-YI
Using patient-led genetics to identify new therapeutic targets in metastatic cholangiocarcinoma

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Background and aims:
Cholangiocarcinoma (CCA) includes a diverse range of biliary malignancies with dismal prognosis. Tumours are often diagnosed when patients present locally-advanced or metastatic disease, limiting the access to potentially curative surgery. The genetic heterogeneity of CCAs has been reported, indicating that the most common gain-of-function mutations in *K-RAS* and *IDH1*, and *FGFR2*-translocations only occur in 16%, 10% and 15% of patients, respectively. These activating mutations exist in a complex genomic landscape where many genes are mutated at low frequencies. The role of these heterogeneously mutated genes in CCA progression is unknown and their potential to modify the effect of more common mutations remains to be studied. Here, we investigate the genetics behind CCA dissemination, describing how cell intrinsic changes impact on cancer cell behavior and shape the tumor microenvironment making it permissive to metastasis.

Method:
Analyzing whole genome/exome sequencing data from 277 patients diagnosed with intrahepatic CCA we identified a patient-led list of CCA mutations. We then developed an *in vivo* screen where we expressed gain of function *K-Ras*^{G12D} with a CRISPR/Cas9 gRNA library targeting genes mutated in the patient data. Immunohistochemistry was performed to characterize the primary and metastatic tumors and their microenvironments. Using CRISPR/Cas9-mediated gene silencing, we interrogated whether these low frequency mutations promote epithelial-to-mesenchymal transition, migration and tumor dissemination in human CCA cells.

Results:
The in vivo screening showed that mutant *K-Ras* in combination with our gRNA library led to tumour development within 8 weeks. Exome sequencing of these tumors identified CRISPR-induced mutations in 53 genes which facilitated mutant *K-Ras*-induced tumor growth. We found a range of chromatin modifiers, including *Ncor1* and *Bap1*, that upon deletion, together with *Tp53* loss and *K-Ras*^{G12D} overexpression, resulted in metastatic CCA. Histological analysis of the primary tumors with metastatic potential revealed phenotypic changes in cancer cells as well as differences in the fibroimmune stroma. Furthermore, deletion of NCOR1 or BAP1 in human CCA cell lines increased their migratory and invasive capacities.

Conclusion:
Low-frequency mutations in chromatin modifying genes, such as *Ncor1* or *Bap1*, cooperate with common driver mutations to promote tumor progression and dissemination by altering cancer cell properties and modifying the tumor microenvironment.

PO1-01-YI
Degradome implications in childhood liver cancer: Identifying CAND1 as a NEDDylation-regulated target in Hepatoblastoma

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Background and aims:
Hepatoblastoma (HB) is the most frequent liver cancer in children, and despite advances in treatment, therapeutic options remain limited for aggressive or relapsed cases. NEDDylation, a post-translational modification regulating cullin-RING ligases, has emerged as a key modulator of protein turnover in cancer. Our previous studies revealed that NEDDylation contributes to HB progression and led to the identification of CAND1 as a novel target regulated by this pathway. CAND1 modulates cullin activity via SCF complexes, which are crucial for protein ubiquitination and degradation. Based on these findings, we aim to explore the functional role of CAND1 and its NEDDylation-mediated regulation in HB progression, to uncover tumor mechanisms and support targeted therapies.

Method:
CAND1 expression was analyzed in HB patient samples and HB-derived organoids through single-cell and bulk transcriptomic profiling. Functional *in vitro* studies were performed in HepT1, HepG2, and HB-284 (PDX-derived) cell lines through siRNA-mediated silencing of CAND1. *In vivo,* HB was induced in C57BL/6 and ^{Bio}NEDD8 mice using the YAPS127A/N90-β-catenin model, followed by CAND1 silencing to assess its effect on tumor and immune response. To further explore the role of NEDDylation in regulating CAND1 function, predicted modification sites were disrupted in mutant constructs and tested *in vitro*.

Results:
CAND1 was significantly overexpressed in HB tissues and organoids, associated with poor prognosis and aggressive subtypes such as C2-pure and Epi-CB. Single-cell analysis confirmed its upregulation in tumor cells. *In vitro* silencing of CAND1 resulted in reduced cellular activity and modulation of molecular markers related to senescence and proliferation. Mutant constructs with disrupted NEDDylation sites exhibited impaired function, supporting the regulatory role of this modification. *In vivo*, tumors from CAND1-silenced mice showed reduced development and an immunomodulatory effect associated with CAND1 targeting.

Conclusion:
These findings position CAND1 as a key regulator of HB progression and immune dynamics. Its modulation by NEDDylation reveals a novel layer of control in tumor biology, supporting its potential as a therapeutic target for aggressive HB subtypes and potentially improving clinical outcomes through combination strategies that enhance treatment specificity while minimizing systemic toxicity in pediatric liver cancer.

PO1-04
The influence of neutrophil migration on HCC in MASLD

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Background and aims:
Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is becoming the leading cause of chronic liver disease and cancer globally [1]. Around 30% of hepatocellular carcinoma (HCC) cases develop on a background of MASLD or the advanced stage (Metabolic Dysfunction-Associated Steatohepatitis (MASH)) [2]. Rates of MASLD and MASH are lower in women compared to men [3]. Neutrophil presence is elevated in MASLD livers and has been implicated in steatosis and inflammation [4]. However, the influence this has in driving the development of MASLD to HCC is not understood. The aim of this work was to examine the effect that key genes for the development and migration of neutrophils, CXCR2 and STAT3, have on the progression of MASLD to HCC.

Method:
Mrp8CreCXCR2$^{fl/fl}$C57BL/6 (CXCR2$^{\Delta neut}$) and Mrp8CreSTAT3$^{fl/fl}$C57BL/6 (STAT3$^{\Delta neut}$) mice were fed a high fat, sugar water diet to examine the extent to which neutrophils contribute to hepatic steatosis. Female CXCR2$^{\Delta neut}$ mice were also fed a high fat diet. Following this, CXCR2$^{\Delta neut}$ and STAT3$^{\Delta neut}$ mice were fed an American Lifestyle-Induced Obesity Syndrome (ALIOS) diet in combination with Diethylnitrosamine (DEN) to assess the contribution of neutrophils to the development of HCC on a MASLD background.

Results:
Body and liver weight of CXCR2$^{\Delta neut}$ mice was significantly decreased compared to wild-type (WT, CXCR$^{fl/fl}$) mice, additionally there was decreased steatosis and inflammation in the livers of these mice. Female CXCR2$^{\Delta neut}$ mice displayed significantly less steatosis and inflammation compared to male mice. When fed a DEN-ALIOS diet, CXCR2$^{\Delta neut}$ mice on anti-PD-1 treatment had a lower tumour burden than WT mice alongside fewer tumour neutrophils. CXCR2$^{\Delta neut}$ mice had a higher proportion of immature neutrophils in the liver. A decreased tumour burden was also evident in STAT3$^{\Delta neut}$ mice compared to WT mice.

Conclusion:
These data demonstrates that restriction of neutrophil release from the bone marrow and subsequent migration inhibits hepatic steatosis, inflammation and tumour growth in a MASLD like context. Furthermore, it re-enforces known observations that females have a level of protection from MASLD. Given recent evidence of the pro-tumoral role of these genes, this work highlights the importance of this signalling pathway not only in a metabolic context, but also in driving the development of HCC.

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[2] Younossi, DOI:10.1097/HEP.0000000000000004
[3] Lonardo, DOI:10.1002/hep.30626
[4] Yilmaz, PMID: 26116591

PO1-06-YI
Unraveling the role of PD-L1 in modulating the immune landscape of cholangiocarcinoma using a human-derived CCA-on-chip platform

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Background and aims:
Intrahepatic cholangiocarcinoma (iCCA) is a highly aggressive tumor of the bile duct epithelium characterized by strong immunoregulatory properties and poor response to conventional therapies. Recent advances combining immune checkpoint inhibitors targeting PD-L1 (e.g., Durvalumab) with chemotherapy (Gemcitabine and Cisplatin), have shown promising improvements in antitumor immune responses. However, patient outcomes remain variable. This study aims to elucidate the role of PD-L1 in shaping the tumor microenvironment (TME) of iCCA and to investigate mechanisms underlying differential treatment responses using a human-derived CCA-on-chip platform.

Method:
Immortalized iCCA cell lines with high (HuCCT1) or low (KKU) PD-L1 expression were cultured in 2D or within the CCA-on-chip platform. Clinical data from iCCA patients (dataset OEP001105) were analyzed using the xCell bioinformatic tool to correlate immune composition and clinical outcomes, while R software was used to generate Kaplan–Meier survival curves. On-chip experiments included live/dead confocal imaging, T-cell migration and cytotoxicity assays, rt-PCR of TME–related genes, and FACS analysis of T cells recovered from the chip.

Results:
Low PD-L1 expression correlated with improved prognosis, while patients with high PD-L1 and low $CD8^+$ T-cell infiltration exhibited the worst survival, identifying PD-L1 as a potential prognostic biomarker. In the CCA-on-chip model, low PD-L1 tumors showed increased immune infiltration and expression of chemoattractant molecules, whereas high PD-L1 tumors upregulated immunosuppressive mediators. T cells recovered from chips with high PD-L1 cells displayed an exhausted phenotype, reduced proliferation, and decreased cytotoxicity. Drug testing revealed that chemo-immunotherapy significantly enhanced T-cell infiltration and reduced tumor viability in high PD-L1 chips compared with chemotherapy alone, whereas low PD-L1 chips showed minimal differences. LDH assays confirmed greater cytotoxic activity in high PD-L1 tumors following combined treatment.

Conclusion:
High PD-L1 expression seems to promote an immunosuppressive TME in iCCA. Blocking the PD-1/PD-L1 axis could restore T-cell activity and enhance antitumor responses, particularly in high PD-L1 tumors. The CCA-on-chip platform effectively models iCCA immune interactions and enables rapid testing of personalized therapeutic strategies, supporting its potential as a valuable tool for precision oncology.

PO1-08
Platelets hijack neutrophils for pro-tumour polarisation in MASH-HCC

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Background and aims:
Platelets and neutrophils are key drivers of MASH and MASH-driven HCC, making them attractive therapeutic targets. Moreover, platelet–neutrophil interactions are known to be pro-inflammatory entities. Therefore, our aim is to decipher the immunological mechanisms by which these interactions, found in both circulation and tumour, are important in tumour progression and cancer therapy resistance, with the objective of targeting them for clinical benefit.

Method:
To generate the MASH-HCC mouse model, C57Bl6 mice were fed a western diet for 12 weeks and the liver was injected with HEP53.4 cells. Treatments were applied at day 21 for 14 days. Neutrophils subtypes in blood were separated using Histopaque gradients, whereas platelets were isolated using Histodenz gradients. Immune cells were stained with flow cytometry antibodies, run in FACSymphony and ImageStream cytometers, and analysed in FlowJo and IDEAS softwares.

Results:
We consistently observe aggregates of platelets at the surface of human HCC neutrophils as well as in mouse models of MASH and liver cancer. The neutrophils are associated with a low-density neutrophil state that is typical of an immunosuppressive myeloid phenotype and characterised by surface expression of the immune checkpoint molecule, PD-L1. We show that exposure of normal density neutrophils to platelets induces a low-density neutrophil phenotype, up-regulation of surface PD-L1 protein expression and enhanced ROS production. In vivo depletion of platelets prevented low density neutrophil formation while neutrophil platelet interaction blockade using anti-CD61 suppressed neutrophil PD-L1 expression in vitro and enhanced anti-PD-L1 therapy in vivo. Closer inspection of neutrophil-platelet aggregates in circulation by image-stream revealed the unexpected observation that PD-L1 is almost exclusively associated with platelets.

Conclusion:
These observations have implications for an ongoing clinical trial (CUBIC) examining the efficacy of a combination of AZD5069, an antagonist of CXCR2-mediated neutrophil trafficking, and durvalumab. We have previously hypothesised that this combination therapy re-programmes neutrophils to anti-tumour phenotype. In the light of our discovery that PD-L1 is almost exclusively found on platelets associated with pro-tumour neutrophils we need to reassess the mechanism by which immune checkpoint interactions modulate neutrophil phenotype in liver disease and further investigate the role of platelet-neutrophil aggregates in tumour immunology.

PO1-09-YI

Prognostic tissue biomarkers for cholangiocarcinoma after tumor resection: from literature review to multicenter international validation

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Background and aims:
Cholangiocarcinoma (CCA) is a heterogeneous group of biliary tumors with poor prognosis and limited treatment options. Potentially curative options include surgical resection; however, recurrence rates remain high. Robust tissue biomarkers to predict patient prognosis after tumor resection are urgently needed. This study aimed to identify and validate prognostic tissue biomarkers by combining mRNA expression and clinical information into machine learning (ML) models.

Method:
A literature review was conducted to identify potential CCA tissue prognostic biomarkers, further validated through Cox PH overall survival (OS) analysis in five transcriptomic cohorts. An international cohort including tumor tissue from 221 patients undergoing tumor resection was collected, and mRNA expression was analyzed by high-throughput TaqMan OpenArray RT-qPCR. Association of variables with recurrence-free survival (RFS) and OS were obtained by Cox PH analyses. Six ML models were trained and evaluated using nested cross-validation. Shapley Additive exPlanations values were used for feature importance and interpretability.

Results:
Among the 496 candidate biomarkers for CCA identified in the literature, 52 harbored prognostic value in the Cox PH analysis in transcriptomic cohorts. In the multicenter validation cohort, Cox PH analyses integrating relevant clinical features and gene expression, revealed 11 genes significantly associated with RFS and 25 with OS. Among six predictive ML models, the random survival forest (RSF) model — combining 9 genes and 4 clinical variables— showed the highest predictive accuracy for RFS, achieving a test AUC of 0.808 and successfully stratifying patients into three groups with different 2-years recurrence risks. *FSCN1*, *LDHA*, and *SLC2A1* emerged as top predictors of recurrence. For OS, the RSF model also showed better performance (test AUC = 0.644), significantly stratifying patients into risk groups with different 5-years OS risk. Top OS gene predictors included *FSCN1, ITGA3,* and *SLC2A1*.

Conclusion:
We identified and validated a robust panel of prognostic tissue biomarkers in CCA patients undergoing surgery. Integration of these biomarkers with clinical variables into ML-based prognostic models enabled

accurate prediction of patient RFS and OS. These models hold promise for improving postoperative risk stratification and guiding personalized surveillance and therapeutic strategies in CCA.

PO1-11-YI
Targeting ferroptosis as a therapeutic vulnerability in preclinical models of cholangiocarcinoma

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Background and aims:
Iron addiction renders cancer cells vulnerable to ferroptotic cell death. This study aimed to evaluate the therapeutic potential of ferroptosis induction in cholangiocarcinoma (CCA), including its link to aggressive stemness-associated traits.

Method:
Kaplan-Meier survival analysis of public datasets evaluated the prognostic significance of stemness and ferroptosis-related markers in CCA. *In vitro* assays were conducted in immortalized normal human cholangiocytes (NHC3) and CCA cell lines EGI1 and HuCCT1. Cells were treated with a ferroptosis inducer, erastin, a solute carrier family 7 member 11 (SLC7A11) inhibitor, to assess effects on colony formation, viability, proliferation, and mitochondrial respiration. In proof-of-principle *in vivo* experiments, a syngeneic orthotopic CCA mouse model was performed by implanting SB1 cells into the livers of C57BL/6 mice. Treatments included vehicle, erastin (15 mg/kg), or the ferroptosis inhibitor ferrostatin-1 (10 mg/kg), administered intraperitoneally 3 times/ week. After 3 weeks, tumor burden and size were assessed, alongside liver and body weight.

Results:
Patients with high expression of stemness markers cluster of differentiation 44 (*CD44*) and POU class 5 homeobox 1 (*POU5F1*), as well as epithelial-mesenchymal transition genes snail family transcriptional repressor 1 (*SNAI1*) and twist family BHLH transcription factor 1 (*TWIST1*) display worse survival outcomes, as did those with elevated anti-ferroptotic *SLC7A11*. *In vitro*, erastin significantly reduced cell viability in cancer cells dose-dependently, while not affecting NHC3. In addition, erastin decreased cancer cell proliferation and colony formation, and altered mitochondrial respiration. *In vivo*, erastin treatment was well-tolerated and reduced tumor size, whereas ferrostatin-1 increased tumor burden and liver-to-body weight ratio, confirming the tumor-suppressive role of ferroptosis.

Conclusion:
Elevated stemness- and ferroptosis-related gene expression correlate with worse clinical outcomes in human CCA. Pharmacological ferroptosis induction successfully restrained tumor growth both *in vitro* and *in vivo*, while its inhibition aggravated tumor burden. These findings highlight ferroptosis modulation as a promising and targetable vulnerability in CCA, warranting further mechanistic and translational studies. (Supported by STSM CA22125, COST; 2023.01547.BD; PTDC/MED-FAR/3492/2021, FCT; LCF/PR/HR21/52410028, "la Caixa" Foundation)

PO1-15-YI

Endoplasmic reticulum-stress as a potential driver of Golgi protein 73 mediated tumor-stromal interactions in hepatocellular carcinoma

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Background and aims:
Hepatocellular carcinoma (HCC) arise in a complex microenvironment where cirrhosis promotes tumor development. The tumor microenvironment (TME), shaped by stromal cells such as hepatic stellate cells (HSCs), sustains fibrosis and progression. Endoplasmic reticulum (ER) stress is emerging as a key cellular process in HCC and TME remodelling. Under stress conditions, accumulation of misfolded proteins activates the unfolded protein response (UPR), to restore homeostasis or induce apoptosis. Golgi Protein 73 (GP73) has been implicated in ER stress transmission in macrophages, but whether it acts similarly in HSCs and how ER stress regulates tumor-stromal interactions remain unclear. This study investigates the role of ER stress and GP73 in modulating the TME and evaluates the effect of ER stress inhibition on HCC progression.

Method:
A chemically induced mouse model for HCC was used and were treated twice per week with ER stress inhibitor AMG-PERK for 3 weeks with liver tissue samples analyzed after 25 weeks. HepG2, Huh7, SNU449 and LX2 cell lines, and patient-derived organoids, were used to assess the effects of ER stress inhibition on HCC development and tumor–stroma interactions.

Results:
Pharmacological inhibition of ER stress with AMG-PERK impede HCC progression in a chemically induced mouse model. Tumor burden, cell proliferation and viability decreased *in vivo*, *in vitro*, and in *ex vivo* organoids. HSCs activation, fibrosis, and inflammation were similarly reduced in the TME. Findings also suggest GP73 as a mechanistic mediator of tumor-stroma interactions triggered by ER stress. Single-cell RNA-sequencing data revealed upregulation of GP73 and PERK in malignant HCC cells, correlating with poor prognosis. GP73 secretion was found to rely on ER stress, binding to extracellular GRP78 to induce PERK-CHOP signaling and support HSCs activation. Transcriptomic profiling further showed that ER stress promotes MYC activation, EMT, and inflammatory pathways, while ER stress inhibition and GRP78-blocking antibodies reversed these effects.

Conclusion:
This study reinforces the central role of ER stress in HCC pathogenesis. Inhibition of ER stress reduced cell proliferation, fibrosis and EMT. GP73 mediates ER stress transmission via GRP78 and PERK signaling, associating tumor stress responses to stromal activation. Inhibition of the PERK-GP73-GRP78 axis suppresses tumor progression and disrupts tumor-stroma crosstalk, highlighting ER stress inhibition as a promising therapeutic strategy in HCC.

PO1-16-YI

Longitudinal high-parameter immune cell phenotyping reveals distinctive polarisation of T-cell immunity associated with relapse following liver resection (LR) for hepatocellular carcinoma (HCC)

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Background and aims:
LR may cure patients (pts) with early-stage HCC, but recurrence occurs in up to 70%. Anti-cancer immunity may influence recurrence although adjuvant immunotherapy has failed to improve such risk. Longitudinal profiling of immune cell phenotype prior to LR and at relapse may dissect distinctive immunological features of pts who relapse versus those cured by LR.

Method:
Between 11/2018 and 11/2021 we prospectively enrolled 19 consecutive pts with *de novo* HCC treated with LR. High-parameter immunophenotyping by Cytometry by Time-Of-Flight was performed on blood samples collected prior to LR and at HCC recurrence or last recurrence-free follow-up. Immune phenotypes pre-LR and at follow-up were evaluated in relationship with relapse, alongside longitudinal patient-level changes in immune cell subpopulations over time. Kaplan-Meier survival analysis was used to evaluate associations with recurrence-free survival (RFS).

Results:
Out of 19 enrolled pts 74% were males, with a median age of 72 years (IQR 62-74). Most pts underwent non-anatomical LR (64%) for unifocal (84%) BCLC 0/A HCC (95%) secondary to cirrhosis (74%) of viral aetiology (58%), all with Child-Pugh A liver reserve. Microvascular invasion (mVI) was found in 1 pt (5%), Edmonson grade was mostly 2/3 (83%). During a median follow-up time of 42 months HCC had recurred in 10 (53%) pts, corresponding to a recurrence rate at 2 years of 46.2% (95%CI 15.7-65.6). At recurrence, patients showed evidence of increase of peripheral CD4+ T effector memory cells re-expressing CD45RA (TEMRA, p=0.03) and activated CD8+ T lymphocytes (p=0.004), not observed in cancer-free patients. At baseline patients with recurrence had higher CD4+ lymphocytes (p=0.04), CD4+/CD8+ ratio (p=0.05), CD8+ CM (p=0.02) and CD8+CM/TEMRA ratio vs cancer-free pts. A higher total CD4+ (p=0.01), CD8+ CM lymphocytes (p=0.02) and CD8+ CM/CD8+ TEMRA ratio (p=0.02) was associated with shorter RFS.

Conclusion:
Evaluation of peripheral lymphocyte subsets prior to LR may aid identification pts with higher risk of HCC recurrence. HCC relapse is associated with an active systemic immune response characterized by CD4 TEMRA and active CD8+ lymphocytes.

PO1-17-YI

Scavenger receptor MARCO acts as a modulator of the immunosuppressive tumor microenvironment and arises as a promising new therapeutic target for hepatocellular carcinoma

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Background and aims:
Hepatocellular carcinoma (HCC) is the most common primary liver tumor and the third leading cause of cancer-related deaths worldwide due to the limited curative options. The innate immune system is crucial for the development of HCC. The macrophage receptor with collagenous structure (MARCO) is a class A scavenger receptor found on specific subsets of macrophages. Recent evidence in solid tumors indicates that MARCO is expressed by immunosuppressive M2-like tumor-associated macrophages (TAMs) in the tumor microenvironment (TME), contributing to immunosuppression and the development and progression of these cancers. However, the role of MARCO in hepatocarcinogenesis remains poorly studied. This study aims to elucidate the role of MARCO scavenger receptor in the development and progression of HCC, as well as its cellular and molecular functions and the molecular mechanisms underlying its regulation.

Method:
The cell-type specific *MARCO* expression was examined in human HCC tumors by using publicly available single-cell RNA sequencing data and *MARCO*-expressing TAMs were phenotypically characterized. mRNA expression of *MARCO* was analyzed in liver tissue samples from healthy individuals and cirrhotic and HCC patients and associated to different immune-functionality scores employing state-of-the-art technologies. To study the role of MARCO in hepatocarcinogenesis, wild type (WT) and *Marco*$^{-/-}$ mice were subjected to a HCC murine model *in vivo* and functional assays were carried out *in vitro*.

Results:
Single cell RNA sequencing data indicate that *MARCO* is mainly expressed by TAMs in HCC and positively correlates with pathways related to cytokine signaling, neutrophil degranulation and epithelial-mesenchymal transition. Bulk transcriptomic analysis show that *MARCO* expression is decreased in human HCC and correlates with worse overall survival. *MARCO* expression levels positively correlate with processes related to immune cell recruitment in HCC. *In vivo*, *Marco*$^{-/-}$ mice are partially protected from DEN-induced HCC. Hepa1-6 HCC cells co-cultured with *Marco*$^{-/-}$ bone marrow derived macrophages (BMDMs) migrate less than the ones co-cultured with WT macrophages.

Conclusion:
MARCO modulates the immunosuppressive TME in HCC, influencing tumor progression by regulating macrophage phenotype, hepatocyte differentiation and immune cell interactions. Subject to further investigation, MARCO may represent a new therapeutic target in HCC.

PO2-3-YI
Platelet C3G restraints liver fibrosis and favours hepatocarcinoma development through the control of macrophage-liver cells crosstalk

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Background and aims:
Hepatocarcinoma (HCC) is usually developed in a chronic liver disease (CLD) context characterized by inflammation and fibrosis that can progress to cirrhosis and HCC. Platelets regulate both fibrosis and HCC development and progression, having opposite effects depending on the context. C3G, a guanine nucleotide exchange factor for Rap1, induces megakaryocytic differentiation and platelet formation, also regulating platelet secretion. Moreover, platelet C3G restraints liver fibrosis and enhances HCC development. Therefore, the aim of this study is to define the mechanisms behind these actions of platelet C3G on CLD.

Method:
We have used megakaryocyte/platelet C3G knock-out (C3G ^{Pf4}KO) mice and their wt counterparts, treated with DEN (diethylnitrosamine) and CCl_4 to induce HCC associated with fibrosis. We have analysed liver immune cells and performed a proteomic analysis of platelet rich plasma (PRP). We have also determined the effect of wt and C3G ^{Pf4} KO platelet secretomes and CXCL7 on different liver cell types *in vitro* (hepatic stellate cells (LX2), macrophages and murine hepatocarcinoma (mHCC) cells), either individually or co-cultured, analysing proteins by immunofluorescence and western blot and mRNAs by RT-qPCR.

Results:
We found that the lack of C3G in platelets reduces the size and number of liver tumours, although it increases fibrosis. Liver immune cell populations were differentially regulated in C3G ^{Pf4} KO mice, highlighting the higher number of macrophages, likely with a pro-inflammatory phenotype. Proteomic analysis of PRPs also showed differences in proteins that regulate the immune response (i.e. CXCL7) and HCC development. *In vitro* experiments revealed that C3G ^{Pf4} KO platelet secretomes activate hepatic stellate cells (HSCs) more than those from wt mice. Furthermore, C3G^{Pf4}KO platelet secretomes also increase cell death in mHCC cells. An indirect crosstalk between macrophages treated with secretomes from wt or C3G^{Pf4}KO platelets and mHCC or HSCs was also observed. In addition, CXCL7, which is enriched in C3G^{Pf4}KO platelets promotes activation of HSCs.

Conclusion:
Our results support that platelet C3G plays a relevant role in HCC, promoting HCC development but protecting from liver fibrosis. These actions might be dependent on the differential C3G-mediated platelet activation and secretion and might rely on the interplay between macrophages, HSCs, HCC cells and other liver cells.

PO2-5-YI
GLUT3-Driven metabolic reprogramming shapes tumor behavior and the immune landscape in intrahepatic cholangiocarcinoma

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Background and aims:
Intrahepatic cholangiocarcinoma (iCCA) is a deadly cancer of the biliary epithelium, with poor prognosis and limited therapeutic options. Tumor metabolic reprogramming is a hallmark of cancer, promoting aggressiveness, therapy resistance, and immune evasion. However, the metabolic drivers of iCCA remain largely undefined. This study investigates the role of glycolysis, focusing on tumor aggressiveness and immune microenvironment interactions.

Method:
Normal cholangiocytes (n=5) and iCCA cells (n=20) were isolated from resected patients at Humanitas. RNAseq identified differentially expressed metabolic pathways. Immunohistochemistry (IHC) was performed on tissue samples from 42 iCCA patients. Functional assays assessed proliferation, migration, and drug response. FACS (n=20) and single-cell RNAseq of $CD45^+$ tumor-infiltrating cells (n=6) characterized immune cell populations. Survival analyses were performed (n=42).

Results:
Firstly, we focused on two main glucose transporters, GLUT1 (SLC2A1 gene) and GLUT3 (SLC2A3 gene). iCCA cells showed downregulation of GLUT1 and marked upregulation of GLUT3 compared to normal cholangiocytes. IHC confirmed GLUT3 expression restricted to tumor cells, while GLUT1 localized in the bile ducts, suggesting iCCA cells acquire GLUT3 expression during tumorigenesis. Furthermore, glucose uptake correlated with SLC2A3 levels, confirming its role in driving enhanced glycolysis in iCCA. Patients with high SLC2A3 expression exhibited significantly higher ^{18}F-FDG uptake on PET, poorer survival, and enrichment of EMT, hypoxia, and glycolysis pathways. To explore the link between glycolysis and tumor aggressiveness, we characterize iCCA cells' behaviour. High GLUT3 cells showed downregulation of mitochondrial complex genes, increased proliferation and migration, EMT marker upregulation, and resistance to gemcitabine/cisplatin in our CCA-on-chip. Finally, given the link between glycolysis and immune suppression, we analyzed the TME: high-GLUT3 tumors exhibited reduced intratumoral $CD8^+$ T cells, while single-cell RNAseq revealed increased PD-1 expression in $CD4^+$ and $CD8^+$ T cells, suggesting an exhausted phenotype.

Conclusion:
iCCA cells acquire GLUT3 to sustain glycolysis, promoting tumor aggressiveness, chemoresistance, and immune evasion. These findings identify GLUT3 as a key metabolic driver and prognostic marker, highlighting its potential as a therapeutic target and supporting future strategies combining metabolic and immune checkpoint inhibition in iCCA.

PO2-6-YI
Metabolic reprogramming in MASH-Related HCC: The emerging role of G6PD as a biomarker and target

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Background and aims:
The incidence of hepatocellular carcinoma (HCC) related to metabolic dysfunction-associated steatohepatitis (MASH) has risen over the past decade and it's correlated to the increasing prevalence of obesity and type 2 diabetes that accelerate liver disease progression and reduce the effectiveness of conventional therapies. Glucose-6-phosphate dehydrogenase (G6PD), a key enzyme of the pentose phosphate pathway (PPP), is essential for NADPH production, redox homeostasis, cell growth, and lipid metabolism. In MASH-related HCC, metabolic alterations enhance the reliance on the PPP, making G6PD a critical point for what concerns tumor survival and progression. Therefore, the aim of the study was to clarify the role of G6PD, focusing on cellular metabolism, oxidative stress and the immune responses.

Method:
For this study were employed a) a cohort of HCC patients with different aetiology and another cohort of MASH patients with advanced fibrosis, carrying or not HCC; b) in vitro models such as HuH7 manipulated in order to overexspress G6PD; c) an experimental murine model subjected to DEN/CDAA protocol to reproduce MASLD related hepatocellular carcinoma.

Results:
Analyses of public databases (TCGA) and clinical cohorts confirm G6PD overexpression in MASH-dependent HCC, which correlates with advanced disease stages, poor prognosis, and aberrant vascular patterns. Both murine and in vitro models demonstrate that G6PD hyperactivity promotes: (i) tumor proliferation, (ii) macrophage polarization toward an immunosuppressive M2 phenotype, (iii) reduced ROS levels (through increased NADPH availability and Nrf2 activation), and (iv) enhanced lipogenesis (via PPARγ, FASN, and SREBP1c) leading to fatty acid accumulation. Finally, the therapeutic potential of G6PD was evaluated using two novel inhibitors (AB109 and AB196), derived from a compound that is already commercially available (G6PDi), that exhibited greater efficacy and potency when compared to the reference drug.

Conclusion:
Thus, G6PD emerges as a promising biomarker and therapeutic target in MASH-related HCC, paving the way for innovative treatment strategies and future translational studies.

PO2-7
HCC immune classification associated with pathological complete response to neoadjuvant therapy

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Background and aims:
Features extracted from the tumor immune microenvironment (TME) are attractive candidates as predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors (ICI). The immune architecture of HCC has been linked to the outcome of checkpoint therapy in patients with advanced disease. In particular, immune-enriched patients are associated with prolonged survival. Here, we sought to evaluate if a simplified immune classification for HCC may predict pathologic outcomes in neoadjuvant therapy.

Method:
Baseline biopsy and resection samples from the PRIME-HCC (NCT03682276) trial (neoadjuvant nivolumab and ipilimumab prior to liver resection in BCLC A patients) were analysed by digital pathology and imaging mass cytometry. Imaging mass cytometry was performed using a 42-plex liver panel published recently and the immune classification was evaluated as described in Salié et al, Gut 2025 using CD8 T cell density and stromal/parenchymal distribution. Radiological (RECIST) and pathological response after resection were independently evaluated.

Results:
Imaging mass cytometry analysis was performed on n=27 baseline biopsy samples. N=7 patients (26%) were classified as immune-enriched, n=10 patients (37%) were identifed as immune-compartmentalized or immune-depleted, respectively. Radiological assessment post-ICI prior to surgery was available in n=25 patients and responses differed between immunotypes, with immune-enriched patients enriched for responders. Specifically, 57% (4/7) patients with an immune-enriched immunotype had PR and 43% (3/7) SD, while one (1/9) patient with an immune-compartmentalized immunotype had a PR and 89% (8/9) SD. In patients with an immune-depleted immunotype we observed one PR (1/9), moreover SD (78%, 7/9), and one PD (1/9). Pathological response data post immune checkpoint therapy data was available in n=20 patients. Patients with the immune-enriched immunotype had significantly higher pathological responses (mean= 97%, SD: ±8.010; 80% (4/6) had complete response) compared to immune compartmentalized (mean= 24%, ±35.026) or immune-depleted patients (mean=13%, SD: ±14.639) patients ($p<0.0001$, ANOVA).

Conclusion:
The immune architecture in HCC is associated with pathological response in neoadjuvant HCC.These data indicate that a simplified immune classification can inform pathological response to neoadjuvant therapy with ICI-based therapies in early HCC which can guide patient selection. It should be further assessed in prospective clinical trials.

PO2-8-YI
KLF15 acts as a tumor suppressor in cholangiocarcinoma by inhibiting cell proliferation, migration, and mitochondrial energetic activity

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Background and aims:
Cholangiocarcinoma (CCA) is a heterogeneous group of biliary malignancies with a poor prognosis. Krüppel-like factors (KLF) are a family of highly conserved and widely expressed transcription factors involved in a multitude of physiological and pathological processes in humans, including cancer. Specifically, dysregulation of expression and/or activity of KLF15 has been reported in several types of cancers but its role in CCA remains unknown. Here, we investigated the role of KLF15 during cholangiocarcinogenesis and evaluated its potential as a prognostic and therapeutic tool.

Method:
KLF15 expression was assessed in human CCA tissues from 10 independent patient cohorts, as well as in human CCA cell lines. KLF15-overexpressing CCA cells were generated through lentiviral transduction. Cells were subsequently characterized for proliferation, survival, tumorigenicity, invasiveness, and overall aggressiveness both *in vitro* and *in vivo*.

Results:
KLF15 expression was downregulated in human CCA tissues across 10 independent patient cohorts, compared to surrounding normal liver tissue or normal bile ducts, independently on the tumor mutational background. Notably, reduced *KLF15* levels correlated with worse overall and recurrence-free survival, was associated with tumor dedifferentiation and negatively correlated with various oncogenic, stemness, and epithelial-to-mesenchymal transition (EMT) markers. Additionally, *KLF15* downregulation was associated with gene hypermethylation in enhancer regions near the promoter in human CCA tumors and *in vitro* treatment with hypomethylating agents (e.g., zebularine) restored *KLF15* expression. *In vitro*, KLF15 protein and mRNA levels were also reduced in human CCA cell lines compared to normal human cholangiocytes (NHC). At the functional level, KLF15 overexpression diminished cell viability, proliferation, tumorigenicity, migration, invasion, and mitochondrial metabolism, without affecting cell death. *In vivo*, KLF15-overexpressing CCA cells exhibited reduced tumor growth rates after subcutaneous injection into immunodeficient mice. Furthermore, intratumoral injection of KLF15-containing lentivirus into pre-established subcutaneous CCA tumors inhibited tumor growth compared to controls.

Conclusion:
KLF15 act as a tumor suppressor in CCA, suggesting its potential as a diagnostic and prognostic biomarker as well as therapeutic target.

PO2-14-YI

Elucidation of the molecular and histological architecture of liver yolk sac tumor and its patient-derived cell line reveals c-MYC–FOXM1 oncogenic dependencies

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Background and aims:
Primary yolk sac tumor of the liver (HYST) is uncommon disease with less than 20 cases reported worldwide and is often misdiagnosed as HCC. Therefore, in-depth molecular and histological characterization of YST and development of representative models are essential for better diagnosis and development of patient-specific therapies.

Method:
Samples of adjacent liver and tumor tissue were collected and processed after surgery. Long-term culture of the primary cell line (PCL) was established. Histological characteristics of tissues and PCL were analyzed by immunohistochemistry (IHC) and immunofluorescence (IF). Key oncogenic networks and actionable mutations were identified by next-generation sequencing (NGS) (DNA/RNA-seq) and single nucleotide polymorphism (SNP) arrays and validated by western blot. Dose-response and synergistic approaches were applied to target the identified onco-networks.

Results:
Tumor tissue showed solid trabecular growth without presence of Schiller-Duval bodies. IF and IHC displayed typical HYST markers (AFP/CK19), which were effectively preserved in xenografts, PCL and spheroids. Transcriptomic profiling confirmed activation of embryonic markers, reduction of macrophages, enrichment of T cells and FOXM1 activation, also sustained in PCL. GISTIC analysis unveiled MYC amplification (8q24.3), validated by WB, as potential regulator of FOXM1. NGS further showed presence of TP53 and KDR mutations which were highly conserved in PCL. Specific targeting of FOXM1-MYC network, as well as KDR mutation, confirmed sustained sensitivity to specific inhibition in PCL.

Conclusion:
For the first time, we were able to dissect HYST at unprecedented molecular level and to establish primary cell line. We identified molecular alterations that could be used for targeted therapy and established cellular model for this extremely rare disease.

PO2-16-YI
Immune Rich, Prognosis Poor? Decoding TLS and CTNNB1 in hepatocellular carcinoma

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Background and aims:
Hepatocellular carcinoma (HCC) demonstrates profound immune heterogeneity, with features of immune activation, exclusion, and exhaustion. Tertiary lymphoid structures (TLS) have emerged as prognostic and predictive markers in solid tumours, yet their role in HCC and their relationship with Wnt/β-catenin signalling remain poorly defined.

Method:
We analysed transcriptomic and clinical data from 370 patients with HCC from The Cancer Genome Atlas (TCGA). TLS scores were generated using a validated nine-gene signature (CXCL13, CCL19, CCL21, LAMP3, CXCR5, CCR7, MS4A1, CD79A, CD79B) via single-sample gene set enrichment analysis. Associations between TLS scores, immune infiltration (ESTIMATE ImmuneScore), immune exclusion/exhaustion gene expression, CTNNB1 mutation status, and clinicopathologic variables were assessed using Spearman correlation, Kaplan–Meier curves, and Cox regression modelling.

Results:
TLS scores strongly correlated with overall immune infiltration (Rho=0.58, p<0.001). High TLS scores associated with cytotoxic lymphocyte signatures but also showed positive correlations with immune exclusion (TGFB1, FAP) and exhaustion markers (PDCD1, LAG3, HAVCR2). On univariable analysis, TLS scores and CTNNB1 mutation status were not significantly associated with overall survival. In multivariable Cox regression including age, sex, stage, grade, CTNNB1, ImmuneScore, and TLS score, only advanced stage independently predicted poor survival (HR 2.62, 95% CI 1.76–3.89, p<0.001). An interaction analysis revealed a trend toward CTNNB1*ImmuneScore (HR 0.46, 95% CI 0.20–1.06, p=0.07), suggesting β-catenin–driven tumours may blunt the prognostic effect of immune infiltration.

Conclusion:
Transcriptome-based TLS signatures in HCC are strongly linked to immune infiltration and correlate with both immune activation and immunosuppressive pathways. TLS scores do not independently predict survival, but their interaction with CTNNB1 mutations highlights the complexity of immune regulation in HCC. Validation against histology is required to confirm the biological relevance of transcriptomic TLS scores, as these cannot distinguish between immature and mature TLS. Integration of spatial immunophenotyping (multiplex IHC, imaging mass cytometry, spatial transcriptomics) will clarify the role of TLS in HCC progression and immunotherapy response.

PO2-17
The DeLIVER Programme: Benefits of live data reporting, quality assurance and analysis

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Background and aims:
We show how clinical capture, to live metrics and researcher querying, can happen seamlessly and in real time, allowing the project team to track progress, avert problematic trial issues, and explore potential hypotheses as the data is acquired and long before the official end of data collection.

Method:
Our approach was applied to the £2.5 million DeLIVER programme, funded by Cancer Research UK. This programme is employing cutting-edge technologies and a multidisciplinary approach to enhance early detection methods for hepatocellular carcinoma (HCC). The programme is in its final year of recruitment and to date has recruited almost 3000 patients from over 40 hospital sites across the UK. Such a large programme requires significant database and informatics support. Not only due to the large number of participants but also the logistics of managing approximately 100,000 sample cryovials and results of associated assays. Our method was to use software packages including REDCap, R, GitLab, cBioPortal, and Shiny, to build an innovative pipeline, taking data collected in the clinic, processing it via nightly run code, and outputing to an interactive dashboard and analysis platform.

Results:
The pipeline produced numerous positive results, including:

1. Data quality checks identified missing data and invalid parameters that would have caused analysis difficulties.
2. Making data available for preliminary analysis resulted in issues being spotted which could then be fixed or mitigated against by amending trial design, ambiguous procedure, or unclear trial questions.
3. Presenting live project data to trial managers enabled planning of future trial steps and reporting on current progress.
4. Collating all outputs from the trial such as clinical data and molecular assay results, onto a single platform gave researchers a one-stop location to explore trial data.
5. Curating raw data files and compressing into downloadable packages for authorised collaborators ensured optimal capitalisation of data and maximised data legacy.

Conclusion:
Live data reporting, QA and analysis is an invaluable approach to clinical trial data management and has been an invaluable part of the landmark DeLIVER programme. By processing data as soon as it is available, quality checking inputs, visualising results, and making data available to stakeholders, multiple opportunities are opened up for liver research and clinical trials in general.

PO3-1-YI

Metabolomic profiling of hepatocellular carcinoma patient sera prior to immune checkpoint inhibitor therapy

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Background and aims:
The combination of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) (A/B) is a first-line treatment for advanced hepatocellular carcinoma (HCC). However, only a subset of patients responds. Emerging evidence suggests that HCC arising in the context of steatotic liver disease is associated with reduced survival following immune checkpoint blockade. We aim to investigate the relationship between serum metabolic profile, underlying HCC etiology and response to A/B.

Method:
We collected patient sera prior to therapy with A/B from 143 prospectively recruited HCC patients from three European centers with different etiologic backgrounds. We performed targeted metabolomics of 1017 metabolites using the MxP® Quant 500 XL kit (biocrates). After data filtering, normalization and batch effect correction, we performed differential and survival analysis to identify predictive biomarker candidates and assess possible correlations with etiology.

Results:
The overall serum metabolic profile does not differ significantly between etiologic backgrounds. The amino acids glutamine and cystine are > 2-fold upregulated in responders to A/B and are associated with longer progression-free survival (PFS, 2.9 vs 8.6 months, and 3.4 vs 8.8 month, each $p < 0.001$). The cholesterol ester CE 20:1 is upregulated in non-responders and patients with non-viral etiology and is associated with shorter PFS (2.3 vs 8.6 months, $p < 0.001$). The candidates remained significant predictors for PFS after adjusting for other prognostic variables, including etiology.

Conclusion:
In our multicenter study, we found slight differences in the serum metabolome with amino acids associated with better response and higher cholesterol levels with earlier progression to A/B. Further validation is needed.

PO3-6
Liver-TRACE: A methylation-based liquid biopsy assay for hepatocellular carcinoma monitoring

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Background and aims:
Effective management of hepatocellular carcinoma (HCC) requires regular assessment of disease progression. However, standard imaging techniques, such as MRI and CT, are costly and resource-intensive, limiting their feasibility for frequent monitoring. These methods are often inaccessible in remote regions and may not detect small tumours under 2 cm, posing challenges for timely evaluation of disease progression. We developed Liver-TRACE, a minimally invasive liquid biopsy assay that quantifies HCC-derived circulating tumour DNA (ctDNA) by detecting tumour-specific DNA methylation marks measured with Oxford Nanopore Technologies sequencing.

Method:
We generated high-resolution methylomes from fluorescence-activated nuclei-sorted HCC and matched hepatocytes, then subtracted features present across a curated atlas of normal human cell types to eliminate non-liver signals. Conserved differentially methylated blocks unique to HCC were aggregated into a single-molecule deconvolution model that classifies cfDNA reads and estimates tumour fraction. Analytical performance was modelled using in-silico admixtures to assess performance metrics (sensitivity/specificity/limit of detection). Clinical benchmarking was undertaken in a pilot cohort (n=132) encompassing 21 healthy controls, 105 HCC and 6 liver metastasis samples.

Results:
At computational benchmarking Liver-TRACE achieved limits of detection between 1-3% tumour fraction with high precision at practical sequencing depths. In the pilot clinical cohort, the assay showed zero false positives among 21 healthy control samples, 100% sensitivity among six liver metastasis samples and ~50% sensitivity among 105 HCC patients across all stages of disease. Assay outputs correlated with tumour burden and stage at diagnosis, supporting biological plausibility.

Conclusion:
Liver-TRACE couples nanopore methylome profiling with single-molecule classification constituting a practical, scalable blood test for monitoring therapy response and recurrence in HCC patients. Its ability to detect disease at low tumour fractions outperforms alpha-fetoprotein (AFP) and may potentially improve current MRI-based disease monitoring. These results support prospective validation in larger, multicentre cohorts. The presentation will detail assay development, analytical validation, and clinical benchmarking.

PO3-7
Functional role of small RNA cluster 1 (smRC1) during hepatocarcinogenesis and angiogenesis

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Background and aims:
Despite the revolution in personalised cancer care, primary liver cancer lacks early detection biomarkers and actionable mechanisms of carcinogenesis are poorly understood. We previously isolated blood extracellular vesicles (EVs) from patients and identified clusters of small non-coding RNA (smRCs) with the ability to accurately detect early-stage HCC (von Felden et al. Gut 2022). Herein, we aim at delineating the functional role of our candidate smRCs during hepatocarcinogenesis.

Method:
In situ hybridization with RNAscope™ on FFPE HCC samples.Lentiviral CRISPR/Cas9-mediated genome editing and validation by RTqPCR.Functional assays: proliferation, cell viability, morphogenesis on Matrigel®, colony formation, cell migration on Transwell®, wound healing.RNA sequencing followed by preranked GSEA exploring MsigDB signatures.EV isolation by MagCapture™ kit. Caspase Glo® 3/7 assay for apoptosis measurement.Epithelial-to-mesenchymal-transition (EMT) markers quantification by Western blot and immunocytochemistry.Angiogenesis markers quantification by RTqPCR.Chick embryo Chorioallantoic Membrane (CAM) Assay for in vivo angiogenesis.

Results:
We confirmed the expression of smRCs in tumour tissues and intratumoural stromal cells via spatial transcriptomic analysis. We established an in vitro model based on the lentiviral CRISPR/Cas9 system to reduce the expression of smRC1 in HCC cells. Functional assays show that smRC1 expression is associated with increased tumour proliferation, morphogenesis, clonogenic ability and migration, as well as EMT. GSEA analysis using MSigDB Hallmarks gene collection set revealed the upregulated pathways in the smRC1 positive cells compared to the knockout: angiogenesis, apoptosis, glycolysis, EMT, among the others (FDR:<0.01). Human Umbilical Vein Endothelial Cells (HUVEC) were treated with smRC1 positive and negative EVs, and conditioned medium, respectively, from the wildtype and knockout HCC clones. EVs and conditioned medium from smRC1+ cells led to increased proliferation, migration, morphogenesis, as well as the upregulation of endothelial activation markers, such as FGFR1, KDR, PECAM and CHD5, in treated HUVEC cells. These findings were confirmed in vivo, in the chick chorioallantoic membrane (CAM) assay.

Conclusion:
Our data suggest a tumourigenic effect of smRC1 expression in HCC cells as well as pro-angiogenic effect of smRC1 on endothelial cells. Successful execution might reveal potential novel therapeutic strategies for primary cancer prevention.

PO3-9
Schlafen 5 potentiates HCC stemness through regulation of CD24 and enhancing glycolysis

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Background and aims:
Hepatocellular carcinoma (HCC) has a high propensity of recurrence and chemoresistance. Hence, deciphering molecular drivers underpinning HCC stemness provides pivotal insights in the treatment perspective. In this study, we aim to investigate the roles of Schlafen 5 (SLFN5) as a novel regulator of HCC stemness.

Method:
SLFN5 expression in HCC clinical samples were examined in public datasets TCGA-LIHC, GSE36376 and GSE124535. Functional effects were studied with in vitro assays using stable SLFN5-knockdown (shSLFN5) and SLFN-overexpressing (SLFN-OE) cells established in human HCC cell lines. In vivo effects on tumor growth and initiation were evaluated with subcutaneous injection mouse models. Proteomic profiles of shSLFN5 and shCtrl cells were analyzed by liquid chromatography-tandem mass spectrometry. Putative binding sites of SLFN5 on promoter regions of downstream targets were predicted based on published data (PMID: 32488136).

Results:
SLFN5 overexpression in HCC tumor tissues was consistently observed in multiple clinical cohorts. A positive correlation was identified between SLFN5 expression and majority of the progenitor cell markers in HCC tissues from the TCGA-LIHC dataset. Knockdown of SLFN5 in HCC cells suppressed cell proliferation and self-renewal ability as demonstrated by cell proliferation assay and tumorsphere formation assay, respectively. Increased apoptosis upon sorafenib treatment was observed in shSLFN5 cells. In vivo tumor growth, tumor incidence and estimated tumor-initiating cell frequency were attenuated upon silencing of SLFN5. In line with the functional phenotypes, CD24+ population was reduced in shSLFN5 cells while increased in SLFN5-OE cells. A total of 534 differentially expressed proteins were identified from the proteomic profiling, and glycolysis was highlighted from pathway analyses. This finding was corroborated by reduced glucose uptake and extracellular acidification ratio in glycolysis upon SLFN5 knockdown. In addition, hexokinase 2 (HK2) expression was downregulated upon silencing of SLFN5 from in vitro and in vivo models. HK2 inhibitor or silencing of CD24 partially abrogated the enhanced self-renewal endowed by SLFN5 overexpression in HCC cells. By ChIP-qPCR assay, SLFN5 bound to one of the 3 and 2 of the 4 predicted sites in the promoter region of HK2 and CD24, respectively.

Conclusion:
SLFN5 governs cancer stemness maintenance in HCC via transcriptional regulation of CD24 and HK2. It is a potential therapeutic target for liver cancer.

PO3-10-YI
Enhanced therapeutic efficacy of doxorubicin–atorvastatin combination therapy in hepatocellular carcinoma

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Background and aims:
Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, largely due to therapeutic resistance and tumor metabolic plasticity. Conventional chemotherapeutics are limited by dose-dependent toxicity and reduced efficacy in tumors with metabolic flexibility. Statins, widely used cholesterol-lowering agents, have emerged as potential adjuvants in cancer therapy due to their ability to disrupt lipid biosynthesis and induce metabolic stress in tumor cells. Here, we explore the therapeutic potential of combining doxorubicin (DOX) with atorvastatin (ATOR) to exploit HCC's dependence on lipid and energy metabolism in HCC models.

Method:
The cytotoxic effects of DOX and ATOR were assessed through dose-response curves and the half-maximal inhibitory concentration (IC50) was calculated, both individually and in combination. Synergism was determined using the Chou-Talalay method. For in vivo validation, a chemically-induced mouse model was employed. DOX and/or ATOR were administered twice weekly for three weeks post-tumor initiation. Liver samples were taken for histological analyses.

Results:
ATOR exhibited potent cytotoxicity in the Huh-7 cell line (IC_{50} = 70.45 µM). When combined with DOX, ATOR markedly enhanced cytotoxicity, reducing DOX's IC_{50} from 165.25 µM to 26.85 µM, indicating a synergistic effect. In vivo, mice with DEN-induced HCC showed a significant decline in body weight compared to healthy mice. DOX treatment further exacerbated this weight loss, whereas ATOR administration restored body weight to levels comparable to those of healthy mice. Histological analyses revealed a decreased tumor burden and number of nuclei following DOX, ATOR, or combination treatment, suggesting reduced tumor cell proliferation. Sirius Red staining and Metavir scoring demonstrated reduced collagen accumulation across all treated groups. Immunohistochemical analyses of LC3B and ATG9A showed that DEN-induced HCC suppressed autophagy, while treatment with DOX and/or ATOR reactivated autophagic processes that will be explored in depth in future studies.

Conclusion:
DOX and ATOR target multiple metabolic pathways crucial for HCC cell proliferation. By inhibiting energy production and disrupting oxidative stress balance, this combination creates a metabolic bottleneck, hindering cancer cell adaptation and growth. Combining statins with chemotherapy exploits HCC's dependence on lipid and energy metabolism, potentially enhancing treatment efficacy and overcoming chemoresistance.

PO3-11
Exploring the bio-mechanics that underpin intrahepatic cholangiocarcinoma initiation.

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Background and aims:
The biliary tree is made of bile ducts – biological tubes formed of a simple biliary epithelia (cholangiocytes) – and their malignant transformation gives rise to cholangiocarcinoma, the second most common primary liver cancer. Cholangiocarcinoma can occur within the intra- (iCCA) or extrahepatic portions of the biliary tree. Fibroinflammatory diseases such as primary sclerosing cholangitis are risk factors for iCCA and are characterised by extensive pathological remodelling and stiffening of the extracellular matrix around the bile ducts. The resulting mechanical stresses inflicted upon biliary cells in these pre-malignant diseases are thought to play a role in malignant transformation, as mechano-signalling is tightly regulated through multiple mechano-transductive pathways (e.g., YAP/TAZ). These pathways remodel cell-cell junctions, the cytoskeleton and the nuclear envelope, which ultimately alter transcription in response to mechanical stress. How this acts in tandem with oncogenic drivers of tumorigenesis remains yet to be studied. We hypothesise that the genetic drivers of tumorigenesis co-operate with and/or alter how cells perceive mechanical cues to alter transcriptional states and cell identity that promote cell survival.

Method:
Cholangiocyte organoids were derived from wild-type (WT) mice and subjected to CRISPR/Cas9 gene editing to knockout *Pten* and *Trp53* (mutant organoids). WT and mutant organoids were subjected to mechanical stress through Forskolin or CFTR-A1 treatment, causing organoid stretch. Following stretch, changes to the phospho-proteome were determined and the transcriptional response through bulk RNA sequencing.

Results:
Mutant organoids display increased nuclear size and reduced circularity in response to stretch. Mechanical stretch induces the expression and activity of classical mechano-sensory molecules, such as actin-binding cofilin and YAP, and over-activation of pathways common in iCCA such as EGFR and MAPK. In response to mechanical stretch, transcriptomic and proteomic analysis revealed a mutant-specific signature. Specifically mechanical stretch of mutant organoids causes dysregulation of the LINC complex. Utilising a single cell transcriptomic dataset from a murine model of iCCA we observe enrichment for dysregulated LINC complex components within mutant cholangiocytes.

Conclusion:
Mechanical stretch of mutant cholangiocyte organoids induces differential gene expression and specifically dysregulation of core components of the LINC complex.

PO4-16
FAM172A knockout activates cellular senescence and suppresses hepatocellular carcinoma by influencing RNA polymerase II pause-release via PHF6

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Background and aims:
Promoter-proximal pausing of RNA polymerase II (Pol II) and its release into productive elongation coordinate chromatin signaling with gene-expression programs. Whether this pause–release axis restricts the senescence program in hepatocellular carcinoma(HCC) remains unknown. Integrating public RNA-seq/ATAC-seq datasets with a drug-induced senescence model, we identified FAM172A and investigated its mechanistic and phenotypic roles in HCC.

Method:
We integrated public GEO bulk RNA-seq and ATAC-seq datasets with transcriptomic signatures of senescence induced by palbociclib or serum deprivation. Chromatin and transcriptional regulation were profiled by ATAC-seq and CUT&Tag for RNA Pol II (total, Ser2P, Ser5P) and histone modifications. Protein interactors were discovered by immunoprecipitation–mass spectrometry (IP-MS) and validated by co-IP. Spontaneous liver tumors from wild-type and knockout mice were analyzed by single-cell RNA-seq and corroborated by flow cytometry. Clinical relevance was evaluated in a human HCC cohort, and in vivo therapeutic silencing was achieved using GalNAc-conjugated siFAM172A.

Results:
FAM172A is upregulated during the induction of cellular senescence but functions as a brake on the senescence program; its loss robustly triggers senescence and the senescence-associated secretory phenotype (SASP). In FAM172A-deficient cells, global chromatin accessibility increases, with marked gains at loci such as TP53, CDKN1A, and CDKN1B. CUT&Tag targeting the Pol II C-terminal domain (CTD) and its phosphorylation sites indicates Pol II pause release and an accumulation of elongating Pol II at key senescence genes. In parallel, H3K4me3 at super-enhancer regions is enriched near these genes, further boosting their expression. IP–MS identified PHF6 as a FAM172A interactor. FAM172A loss inhibited PHF6 ubiquitination and enhanced Pol II pause-release via its second PHD domain. In vivo deletion of FAM172A reduced NK cells and increased myeloid cells and lowers tumor burden; in clinical specimens, FAM172A is highly expressed and associated with poor prognosis. Therapeutically, GalNAc-siFAM172A efficiently silences the target gene in the liver, reduces tumor number and volume, and prolongs survival.

Conclusion:
FAM172A is a chromatin-associated factor that regulates Pol II pause-release through PHF6. Inhibition of FAM172A promotes cellular senescence and suppresses HCC progression. GalNAc-siFAM172A provides a feasible liver-targeted therapeutic strategy for HCC.

PO5-1
Single-cell RNA sequencing reveals molecular concordance between circulating tumor cells and primary tumor nuclei in hepatocellular carcinoma

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Background and aims:
Circulating tumor cells (CTCs), shed from primary tumors into the bloodstream, represent promising biomarkers for cancer diagnosis and prognosis. Despite recent advances in CTC quantification, comprehensive molecular characterization of these cells remains limited. This study aimed to establish a robust workflow for the isolation and transcriptomic profiling of CTCs to elucidate their molecular features and role in hepatocellular carcinoma (HCC) progression.

Method:
Eighteen patients with HCC undergoing surgical resection were prospectively enrolled. Peripheral blood was collected at baseline and every three months during follow-up. Mononuclear cells were isolated, CD45-positive cells depleted, and the remaining cells were labeled with EpCAM, Pan-Cytokeratin, and Glypican-3 for FACS sorting and quantification.

Whole-transcriptome sequencing was performed on six paired CTC and tumor nuclei samples from early-stage HCC patients. Tumor nuclei were isolated from fresh-frozen tissue and analyzed using the Rhapsody system for single-cell transcriptomics and copy number variation (CNV), with cell annotation based on reference liver and tumor datasets.

Results:
CTC levels showed no significant fluctuations during the 12 months following resection; however, their percentage was an independent risk factor for HCC recurrence. Single-cell RNA sequencing (scRNA-seq) of CTCs revealed a distinct profile with high expression of hepatic (HSPA1A, KRT8, GPC3) and epithelial (EPCAM) markers. An average of 10.3 ± 3.3 CTCs per sample was identified, with CNV analysis confirming high aneuploidy. Single-nucleus RNA sequencing of matched tumor tissue identified tumor, immune, Kupffer, stellate, and endothelial cells, with tumor cell proportions ranging from 5.2% to 51.3%. Comparative analysis showed ~50% overlap in top expressed genes between CTC and tumor clusters.

Conclusion:
This preliminary study demonstrates that single-cell RNA sequencing enables precise molecular discrimination of CTCs from other circulating cell types. By capturing tumor-specific transcriptional and genomic features non-invasively, this approach offers a powerful tool to characterize tumor heterogeneity and the intratumoral microenvironment without the need for invasive biopsies.

PO5-3-YI

Mitochondria-dependent STING activation enhances immune remodeling and cabozantinib response in hepatocellular carcinoma

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Background and aims:
Cabozantinib is a tyrosine kinase inhibitor (TKI) used to treat advanced hepatocellular carcinoma (HCC), but its benefits are still limited. A better understanding of how it shapes the immune response, especially through mitochondrial stress and the cGAS/STING pathway, could help improve its therapeutic impact.

Method:
Cabozantinib's effects on mitochondrial integrity and innate immune signaling were analyzed in hepatoma cells and macrophage cell lines, measuring mitochondrial depolarization, reactive oxygen species production, cytosolic release of mitochondrial DNA (mtDNA), activation of the cGAS/STING pathway and expression of type I interferon-stimulated genes (ISGs). CRISPR-mediated STING knockdown and mtDNA depletion were evaluated. Cabozantinib and the STING agonist vadimezan were examined in an immunocompetent mouse model. Translational relevance was assessed by multiplex proteomic profiling of serum samples from 18 cabozantinib-treated HCC patients across two independent cohorts.

Results:
Cabozantinib induced mitochondrial depolarization, oxidative stress, and cytosolic mtDNA release, resulting in STING-dependent signaling and ISG upregulation in hepatoma cells. Disruption of mtDNA or STING signaling abrogated these effects. In vivo, cabozantinib reduced tumor growth and promoted

$CD8^+$ T cell and NK cell infiltration, which were further enhanced by vadimezan co-treatment. Patient serum proteomics revealed consistent increases in immune and stress-related proteins (e.g., granzyme B, HO-1, CAIX, CXCL13) and decreases in angiogenic and immunosuppressive factors (e.g., VEGFR-2, ANGPT1/2, CCL17), paralleling the systemic immune remodeling observed in preclinical models. Baseline immune signatures were associated with clinical outcome.

Conclusion:
Cabozantinib induces immune response depends on mitochondrial disruption and cGAS/STING activation, leading to immune remodeling in HCC. These findings provide insights into the immunomodulatory effects of cabozantinib, support combinations with STING agonists for treatment and suggest candidate biomarkers for predicting therapeutic response in TKI-treated patients.

PO5-5-YI

Humanised orthotopic tumours offer a physiologic model of human hepatocellular carcinoma and improved ex vivo therapeutic screening

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Background and aims:
Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and diagnoses typically occur during advanced stages of disease, at which point therapeutic intervention is limited to a small number of systemic regimens. Immunotherapy is the first-line treatment for advanced HCC, although this only extends lifespan by a few months in a minority of patients. There is therefore an unmet need for novel HCC therapies, and by extension preclinical research into HCC. We aim to engineer humanised mouse models of HCC which provide a realistic reflection of human disease whilst modelling HCC in the context of a whole organism. Generation of precision-cut tumour slices (PCTS) from the tumours would then offer an *ex vivo* system in which to probe disease mechanisms and screen novel therapies.

Method:
Human orthotopic HCC tumours were generated via intrahepatic injection of $1x10^6$ HuH7 or HepG2 cells in MISTRG mice. HCC cells were transfected to secrete luciferase and were injected as either monocellular or multicellular suspensions in combination with the hepatic stellate cell line LX2. Humane endpoints were determined via CT imaging, at which point the tumours were harvested and used to generate PCTS. Resultant PCTS were cultured for up to 8 days *ex vivo*, in which time luciferase assays, resazurin assays, cytotoxicity assays and ATP measurements were performed to ascertain tissue viability. PCTS were also treated with 10μM sorafenib to assess the ability to target human PCTS therapeutically.

Results:
LX2 cells were necessary to provide the structural integrity required for PCTS generation, while monocellular HCC tumours did not yield reproducible PCTS. The metabolic activity of the resulting HuH7:LX2 and HepG2:LX2 PCTS were maintained throughout the 8-day culture, whilst an increase in ATP production and luciferase secretion was observed, and the cytotoxic effects following the tissue slice process subdued after day 1. Treatment with sorafenib resulted in a complete loss of viability after 3 days, with the luciferase readout providing a longitudinal assessment of therapeutic response.

Conclusion:
Orthotopic engraftment of MISTRG mice with human HCC enables the growth of human tumours, and offers an *ex vivo* system to screen a greater number of therapeutic strategies using fewer tumours in the context of human disease. Future development using patient-derived HCC cells and mice with reconstituted human immune systems will further enhance the physiological relevance of the model.

PO6-5-YI

A comparative study of idarubicin and doxorubicin in a chemically-induced in vivo mouse model for hepatocellular carcinoma

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Background and aims:
Hepatocellular carcinoma (HCC) remains a major therapeutic challenge with limited systemic treatment options and suboptimal response rates. Anthracyclines such as doxorubicin (DOX) and idarubicin (IDA) are frequently used in clinical settings, including transarterial chemoembolization (TACE), yet their efficacy and adverse effects in HCC remain poorly defined.

Method:
In this long-term *in vivo* study, we performed a head-to-head comparison of DOX and IDA in a chemically induced mouse model of HCC, using repeated dosing (twice weekly for three weeks) to mimic clinical exposure similar to TACE.

Results:
Both treatments induced significant weight loss and spleen enlargement, with IDA exhibiting a more pronounced systemic impact. While neither compound significantly altered tumor burden, both agents unexpectedly reduced hepatic collagen deposition and fibrosis. Mechanistically, DOX decreased hepatic stellate cell (HSC) activation without major changes in fibrotic markers, whereas IDA paradoxically increased HSC activation and upregulated *TGF-β* and *CTGF* expression. Both DOX and IDA activated endoplasmic reticulum (ER) stress pathways in non-tumorous liver tissue, particularly through the PERK axis. IDA treatment was associated with a strong upregulation of *ATF4* in hepatocytes and enhanced macrophage recruitment, suggesting an impact on the hepatic microenvironment.

Conclusion:
Despite comparable tumor control, the divergent stromal and inflammatory responses may help explain differences in toxicity and long-term outcomes observed clinically. Our findings emphasize the need to consider microenvironmental and stress-related pathways when selecting and optimizing anthracycline regimens for TACE.

PO6-6
A data-driven precision medicine framework for primary liver cancer: insights from the Liver Cancer Collaborative

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Background and aims:
Primary liver cancer (PLC) rates are projected to increase, highlighting the need for better strategies to reduce morbidity and mortality. However, limited availability of biological material from patients with intermediate and late-stage disease has significantly impacted this endeavour. To address this, the Liver Cancer Collaborative (LCC) sought to i) determine the safety of routine tumour biopsies for improved diagnostic certainty and for research, ii) build a comprehensive biorepository of patient samples, iii) undertake RNA, single cell and whole exome sequencing (WES) and iv) establish a secure Digital Research Environment (DRE) to link comprehensive and longitudinally collected clinical data with key research data.

Method:
Participants with PLC were enrolled from tertiary hospitals in Perth, Australia, between 16.12.20 and 31.7.25. Biospecimens were collected at the time of planned interventions. Clinical data was extracted from EHR, clinical assessments, and laboratory results at baseline and during follow-up. Sequencing data were processed through standardised pipelines. All data were uploaded into the DRE for processing and made available for further research via F.A.I.R. access.

Results:
We established a biorepository of 373 participants (212 percutaneous tumour biopsies, 52 resections, and 116 blood-only samples). WES, RNA, and single-cell sequencing have been performed on these samples. These data in conjunction with detailed clinical data, are accessible in our DRE where they can be used to explore molecular aspects of liver cancer tumorigenesis, as well as provide evidence-based information to support clinical decisions.

The LCC Data Safety Committee has thus far reviewed 174 patients who have undergone a percutaneous tumour biopsy, with follow-up periods ranging from 8 to 44 months and an average of 5.9 cores per patient. Low rates of extended hospital stay (1.1% of participants), needle track seeding (1.1%), intraprocedural haemorrhage (1.1%), and unplanned hospital readmission (1.1%) were identified. No biopsy-related mortality was observed.

Conclusion:
We have demonstrated that routine tumour biopsy for primary liver cancer is feasible, safe and provides a critical resource for liver cancer research. Our extensive biorepository currently supports twelve research projects spanning clinical decision making, biomarker validation and discovery research. Outcomes from this research are expected to significantly impact the management and treatment of primary liver cancer.

PO6-7

Prognostic value of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in hepatocellular carcinoma: a study on relapse-free survival and overall survival after hepatectomy or transplantation

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Background and aims:
Local and systemic inflammation are recognized as hallmarks of cancer, playing a critical role in the pathogenesis and progression of hepatocellular carcinoma (HCC). Inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have emerged as potential prognostic indicators in HCC patients undergoing hepatectomy or liver transplantation. This study aimed to evaluate the prognostic significance of NLR and PLR in predicting relapse-free survival (RFS) and overall survival (OS) among patients with HCC treated with either hepatectomy or orthotopic liver transplantation (OLT).

Method:
We conducted a multicentre retrospective cohort study involving 74 individuals diagnosed with HCC (64 males; 86.5%). NLR and PLR were recorded preoperatively and at 1-, 3-, 6-, and 12- months postoperatively. Cox proportional hazards multivariate regression analysis was performed using OS and RFS as dependent variables, with NLR, PLR, and type of surgery as independent variables. Repeated measures ANOVA was used to assess longitudinal changes over time. All statistical analyses were conducted with SPSS version 26.0.

Results:
Reduced RFS was independently associated with hepatectomy (HR: 7.105–11.436, $p \leq 0.001$), elevated NLR at 3- and 12- months postoperatively (HR: 1.514–1.452, $p \leq 0.003$), and PLR at 12- months (HR: 1.009, $p = 0.023$). Each unit increase in NLR above 2.5 significantly correlated with reduced RFS ($p = 0.003$). Similarly, reduced OS was independently associated with hepatectomy (HR: 6.134–17.312, $p \leq 0.008$), increased NLR (HR: 1.517–1.767, $p \leq 0.002$), and PLR (HR: 1.010, $p = 0.008$), with NLR >2.5 remaining a significant predictor ($p = 0.002$). Among patients undergoing hepatectomy, reduced RFS was significantly associated with elevated NLR at 3 and 12 months (HR: 1.426–1.702, $p \leq 0.022$) and with PLR at 12 months (HR: 1.008, $p = 0.033$). No statistically significant associations were identified in liver transplant recipients.

Conclusion:
Elevated NLR values at 3- and 12- months postoperatively, as well as elevated PLR at 12- months, were independently associated with shorter RFS and OS in patients with HCC, particularly among those undergoing hepatectomy. These findings underscore the potential use of NLR and PLR in clinical decision-making as biomarkers for risk stratification and outcome prediction in HCC management, warranting further investigation in prospective studies.

PO6-8-YI

Aptamer-mediated blockade of HuR SUMOylation disrupts cholesterol metabolism and tumor progression in hepatocellular carcinoma

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Background and aims:
Human antigen R (HuR/ELAVL1) is an RNA-binding protein that stabilizes oncogenic transcripts involved in proliferation, angiogenesis, and metabolic adaptation. In hepatocellular carcinoma (HCC), HuR overexpression correlates with poor prognosis. SUMOylation of HuR enhances its affinity for oncogenic mRNAs and promotes metabolic rewiring, including activation of the mevalonate pathway, which is frequently upregulated in HCC, providing essential intermediates for tumor growth, metastasis, and immune evasion. Aptamers, highly specific nucleic acid ligands, offer a novel strategy to inhibit HuR SUMOylation. The aim of this study was to determine whether aptamers specifically blocking HuR SUMOylation could impair tumor metabolism and growth in HCC.

Method:
Aptamers targeting HuR SUMOylation sites were generated by SELEX and tested in Huh7 cells expressing wild-type or SUMOylation-deficient mutant of HuR. Effects on proliferation, senescence, oxidative stress, mitochondrial function, and cholesterol metabolism were evaluated by crystal violet staining, β-galactosidase assay, MitoSOX, MitoTracker, Seahorse analysis, qPCR, Western blot, and protein/RNA immunoprecipitation. *In vivo* efficacy was assessed in Huh7 xenograft assay in NSG mice (n = 6).

Results:
Aptamer treatment markedly inhibited cell proliferation by approximately 70% and increased senescence markers, including p21, phospho-histone H2AX, and β-galactosidase activity. Treated cells showed elevated ROS levels and reduced oxygen consumption and glycolytic capacity, consisting with mitochondrial dysfunction. Transcript analysis revealed a general downregulation of key genes involved in cholesterol synthesis and uptake (*HMGCR, HMGCS, SREBF2, PCSK9, LDLR*, and *LIPA*) after aptamer treatment. Moreover, aptamers reduced HuR RNA-binding affinity to targets related to cholesterol metabolism and cell proliferation. *In vivo*, aptamer administration slowed tumor growth by approximately 60% compared with controls.

Conclusion:
SUMOylated HuR acts as a key regulator linking post-transcriptional control and metabolic adaptation in HCC. Pharmacological blockade of HuR SUMOylation with aptamers disrupts cholesterol biosynthesis and tumor progression, providing proof-of-concept for an innovative metabolic-targeted therapeutic strategy in advanced HCC.

PO6-10-YI
Exploring the prognostic significance of miR-1973 and snoRNAs in hepatocellular carcinoma: a preliminary study

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Background and aims:
Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality. Identifying reliable prognostic markers is crucial for optimizing personalized treatment strategies, enabling early intervention, and improving both survival rates and patient outcomes. MicroRNAs (miRNAs) and small nucleolar RNAs (snoRNAs) are non-coding RNAs that have shown promise as biomarkers for cancer progression. The potential regulatory and prognostic relationship between miR-1973 and two snoRNAs, snoRA47 and snoRD126, remains unexplored. This study aims to evaluate the expression profiles of miR-1973 in combination with snoRA47 and snoRD126 to assess their association with clinical outcomes such as with time to recurrence (TTR) and disease-free survival (DFS).

Method:
We analyzed tissue samples from 34 HCC patients to quantify miR-1973, snoRA47, and snoRD126 expression. miR-1973 was assessed using microarray profiling, while snoRNA levels were measured by RT-PCR. Spearman correlation was used to evaluate relationships between miR-1973 and the snoRNAs. Kaplan-Meier survival analysis was used to assess the relationship between marker expression and clinical outcomes, including time to recurrence (TTR) and disease-free survival (DFS). Additionally, Cox regression analysis was employed to evaluate how these markers influence the risk of cancer recurrence and disease progression.

Results:
miR-1973 showed a significant positive correlation with snoRA47 (rho = 0.42, p = 0.02) and snoRD126 (rho = 0.57, p = 0.0004). Cox regression analysis demonstrated that patients with high expression of both miR-1973 + snoRA47 were associated with worse clinical outcomes such as TTR and DFS (HR = 11.3, 95% CI: 1.33–95.7, p = 0.03) and (HR = 3.38, 95% CI: 1.08–10.6, p = 0.03). A similar trend was observed for miR-1973 + snoRD126 (HR = 9.56, 95% CI: 1.13–80.9, p = 0.04) for TTR and (HR = 9.56, 95% CI: 1.13–80.9, p = 0.04) for DFS, although not significant.

Conclusion:
The preliminary findings suggest that the combination of miR-1973 with snoRA47 or snoRD126 shows promise as a prognostic biomarker for early recurrence in HCC.

PO7-1
A novel cyclodextrin with improved safety profile for targeting hepatocellular carcinoma

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Background and aims:
Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide and treatment options remain limited, underscoring the need for novel therapeutic strategies. Hyperlipidaemia and intracellular cholesterol accumulation are reported to be crucial contributors in the development and progression of HCC. Cyclodextrins are cholesterol-depleting agents and have shown anticancer effects, but conventional 2-hydroxypropyl-beta-cyclodextrin (HPbetaCD) is limited by toxicity due to plasma cholesterol extraction. In the current study, we investigated a novel polymeric gamma cyclodextrin (HPgammaCDP) that targets intracellular cholesterol without depleting membrane cholesterol, as potential new treatment for HCC. We hypothesized that HPgammaCDP inhibits progression of HCC by depleting cholesterol without inducing toxicity.

Method:
Plasma membrane cholesterol extraction was examined in Raw 264.7 macrophages. Cell viability assays were performed in Raw 264.7 macrophages and HepG2 liver cancer cells. To further compare safety profiles of the beta and gamma cyclodextrin, zebrafish larvae were exposed to HPbetaCD or HPgammaCDP and survival was monitored. Antitumour activity was evaluated in vivo using a chorioallantoic membrane (CAM) assay, in which HepG2 cells were engrafted onto chicken embryo membranes.

Results:
In line with our hypothesis, HPgammaCDP did not extract cholesterol from the plasma membrane and preserved Raw 264.7 macrophage and HepG2 viability, in contrast to HPbetaCD. Consistently, whereas treatment of HPbetaCD at a dose of 15mg/mL impaired survival of zebrafish larvae, HPgammaCDP did not impact zebrafish viability. Yet, stand-alone treatment with either HPbetaCD or HPgammaCDP significantly reduced tumour size in the CAM assay, indicating that HPgammaCDP exerts comparable antitumour efficacy while sparing normal tissues, thereby demonstrating a potential broader therapeutic window.

Conclusion:
HPgammaCDP reduced HCC tumour size in vivo without exhibiting toxicity supporting its potential as a novel, safer cyclodextrin-based therapy. Ongoing studies aim to further evaluate HPgammaCDP as a candidate for (adjuvant) HCC treatment.

PO7-2-YI

Identification of lncRNA signature involved in the effectiveness of tyrosine kinase inhibitors in cultured liver cancer cells

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Background and aims:
Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the third leading cause of cancer-related mortality worldwide. Current systemic therapies for HCC include Atezolizumab+Bevacizumab, and tyrosine kinase inhibitors (TKIs) such as Sorafenib and Lenvatinib. Long non-coding RNAs (lncRNAs) have emerged as key regulators of tumor progression and therapeutic response. The aim of the study was the identification of functional relevant lncRNA signature in liver cancer cells under treatment with TKIs.

Method:
RNA-seq was performed in a well-differentiated hepatoblastoma HepG2 cell line, and metastatic SNU449 liver cancer cells under Sorafenib treatment. Sorafenib significantly downregulated the expression of seven lncRNAs. The functional impact of downregulated lncRNAs was assessed using the PiggyBac transposon overexpressing system in cell migration and cell proliferation in liver cancer cells under Sorafenib and Lenvatinib-treated cells.

Results:
RNA-seq analysis identified seven lncRNAs (KDM5A, CCDC22, MIRLET7IHG, BCAN-AS1, AL162458, LINC03015 and RAD51-AS1) that were significantly downregulated by Sorafenib in HepG2 and SNU-449 cell lines. The overexpression of KDM5A and CCDC22 increased cell migration in control and Sorafenib- and Lenvatinib-treated cells. Furthermore, the overexpression of CCDC22, BCAN-AS1, AL162458 tend to increase cell proliferation in control and Sorafenib- and Lenvatinib-treated cells.

Conclusion:
1. The downregulation of KDM5A and CCDC22 was involved in the reduction of cell migration by TKIs in SNU449 liver cancer cells.
2. The downregulation of CCDC22, BCAN-AS1 and AL162458 might be also involved in the reduction of cell proliferation by TKIs in SNU449 liver cancer cells.
3. **Future perspectives**: Ongoing studies in a more complex 3D culture system constituted by liver cancer cells with stromal cells might emphasize the relevance of the lncRNA signature in cells under Atezolizumab+Bevacizumab treatment.

PO7-11
JMJD2A epigenetically regulates hepatocellular carcinoma metabolism

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Background and aims:
Hepatocellular carcinoma (HCC) is an aggressive malignancy that marks the sixth most common cancer worldwide. Regardless of aetiology, progression of HCC is variable and influenced by non-genetic factors, pointing to its epigenetic nature. Our initial aim was to characterize epigenetic modifications involved in HCC development and evaluate their potential as therapeutic targets. Our final goal is to explore the therapeutic potential of JMJD2A targeting, using inhibitors and/or microRNA mimics, by employing a novel liver cancer-on-a-chip technology.

Method:
We have established four liver cancer cell lines resistant to three chemotherapeutic drugs in which we performed transcriptomic profiling. We have also employed a series of functional assays following JMJD2A knockdown to confirm its oncogenic properties. Specifically colorimetric and luminescence-based cell growth assays as well as spheroid formation assays. Furthermore, we have employed RNA-seq and inmunohistochemistry in tissues to confirm JMJD2A correlation with HCC progress.

Results:
Transcriptomic profiling revealed up-regulation of lysine demethylase JMJD2A in chemoresistant cells. JMJD2A knockdown significantly suppressed liver cancer cell growth. Similarly, stem cell properties were also affected by JMJD2A knockdown, as assessed by spheroid formation assays and expression analyses of cancer stem cell markers. Importantly, RNA-Sequencing profiling and bioinformatic analyses revealed that metabolic pathways are predicted to be significantly dysregulated. We have further employed microRNA profiling and identified microRNA-137 (miR-137) as a possible regulator of JMJD2A expression. The regulatory role of miR-137 was verified by RT-qPCR and western blot. Finally, through immunohistochemical and RT-qPCR analyses, we show that JMJD2A expression is increased in liver cancer tissues and positively correlated with disease progression.

Conclusion:
Thus far, we have confirmed the oncogenic role of JMJD2A in HCC as well as its impact in cancer cell stemmness and cancer cell growth. We have also confirmed regulation from microRNA-137 onto JDMJD2A and the positive correlation between JMJD2A expression and disease stage.

PO7-12-YI

Identification of TOP2A, CDC20, and CCNB1 as novel biomarkers for early detection and prevention of liver cancer through bioinformatics analysis of genomic and transcriptomic data

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Background and aims:
Liver cancer remains a major public health challenge in West Africa, particularly in Nigeria, where late diagnosis and limited access to effective screening contribute to high mortality. The discovery of reliable biomarkers is essential for early detection and prevention, improving timely intervention and survival outcomes. This study aimed to identify novel molecular biomarkers for early detection and prevention of liver cancer using integrated bioinformatics analysis of genomic and transcriptomic data.

Method:
Publicly available datasets from The Cancer Genome Atlas (TCGA) and the Gene Expression Omnibus (GEO) were analyzed, comprising approximately 500 liver cancer and 200 normal tissue samples. Differential gene expression analysis was performed using DESeq2, followed by pathway enrichment analysis via Reactome and protein–protein interaction network analysis using STRING.

Results:
Genes with fold change >1.5 and adjusted p-value (FDR) <0.1 were considered significant. The analysis identified three key genes—**TOP2A**, **CDC20**, and **CCNB1**—which were significantly overexpressed in liver cancer compared to normal tissues. Functional enrichment revealed their involvement in cell cycle regulation, mitotic processes, and DNA repair pathways, indicating potential roles in hepatocarcinogenesis

Conclusion:
These findings suggest that TOP2A, CDC20, and CCNB1 may serve as robust biomarkers for early diagnosis and prevention of liver cancer. Further experimental and clinical validation could support their use in biomarker-based screening and targeted intervention strategies, particularly in high-burden regions such as West Africa.

Key words: Liver cancer; Biomarkers; Bioinformatics; Gene expression; Early detection

PO7-13-YI
Targeting the mdm2-p53 axis to restore tumour suppression and reprogramme the immune microenvironment in hepatocellular carcinoma patient-derived models and precision cut slices

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Background and aims:
It is well known that the tumour suppressor p53 is a master regulator of cell fates, with over 3000 target genes involved in classical pathways such as cell cycle arrest, apoptosis and senescence, but more recently it has been unveiled that p53 is a major contributor to cellular processes like metabolism, autophagy, ferroptosis, metastasis and immunity. Hepatocellular carcinoma (HCC) is an aggressive form of liver cancer that results in over 5000 deaths annually across the UK with around 30-60% of patients having mutations in the *TP53* gene. *TP53* mutations are highly likely to result in a destabilised and inactive form of the wild-type protein whereby p53 is unable to halt the cell cycle or induce cell death resulting in uncontrolled malignant cell proliferation: creating a more aggressive phenotype with a pro-tumorigenic immune microenvironment. Despite some patients carrying wild-type forms of p53, overexpression or amplification of the negative regulator Mdm2, has also been observed correlating to poorer patient survival. With decades worth of research demonstrating the role of the p53 pathway in both cancer progression and senescence, p53 activation via the inhibition Mdm2 represents a valuable therapeutic strategy.

Method:
Utilising a library of HCC patient-derived cell lines, various Mdm2 inhibitors were applied to 2-dimentional cells *in-vitro* whereby cellular proliferation, viability and toxicity were analysed as well as induction of senescence via beta-galactosidase staining.

Results:
Restoration of p53 activity by Mdm2 inhibition did not affect cellular toxicity, viability or metabolic across all primary lines however, proliferation was significantly decreased suggesting that Mdm2 inhibition may induce senescence amongst HCC cells.

Conclusion:
Based on these preliminary findings, proliferation, senescent and apoptotic protein levels will be confirmed using western blots along with gene expression profiles using qPCR. In addition, an *ex-vivo* precision cut tumour slice system, generated from orthoptic tumours, will be used to study the tumour microenvironment and immune cell composition in response to Mdm2 inhibition and restoration of p53 activity. By harnessing tissue clearing methods and 3-dimentional confocal imaging we aim to produce high-quality and single-cell resolution images that showcase the reprogramming of the immune TME in response to Mdm2 inhibition.

PO7-14-YI
TROP2 expression correlates with poor survival and activation of cancer stem cell-like features in BTC

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Background and aims:
Biliary tract cancer (BTC) comprises a heterogenous group of malignancies originating from biliary tract epithelium partly through a stepwise process involving Biliary Intraepithelial Neoplasia (BilIN). The human trophoblast cell-surface antigen 2 (TROP2) is an emerging therapeutic target and regulator of several crucial cellular processes including stem cell properties. This study investigates expression of TROP2 and its role in development and progression of BTC.

Method:
Immunohistochemical staining was used to assess TROP2 expression as well as immune cell infiltration (CD4+ / CD8+ / CD20 + / CD25 + / CD68 + /FoxP +) in BTC tissue samples (n = 518) and corresponding BilIN lesions (n = 159) and correlated with survival data. RNA sequencing data from BTC patients (n = 126) from MASTER DKTK/NCT cohort underwent Gene Set enrichment analysis (GSEA). Optimal cutoff calculation for TROP2 transcripts per million (tpm) and estimated protein activity (mVIPER analysis) were employed to assess associations between TROP2 expression/activity and overall survival (OS). Immune cell infiltration was estimated using xCell2-based immune deconvolution.

Results:
Dynamic changes in TROP2 expression were observed between matched precursor BilIN lesions and invasive BTC (45% increase in TROP2 expression; 28% decrease). Low TROP2 expression correlated with improved OS in BTC patients (3.5 vs. 2.1 years HR 1.4 [95% CI 1.1–1.8]), but no such correlation was evident in the BilIN cohort. In the MASTER BTC cohort, patients with low TROP2 mRNA levels or low TROP2 activity demonstrated significantly longer OS (6.4 vs. 2.2 years, HR 2.4 [95% CI 1.4–3.8] and 4.6 vs. 2.1 years, HR 1.84 [95% CI 1.2–2.9]). GSEA analysis revealed enrichment of predefined inflammatory and stemness-associated gene signatures in TROP2-high tumors. Assessment of apparent immune cell infiltration as well as immune deconvolution revealed no differences in immune cell infiltration, indicating a cell-intrinsic, autonomous inflammatory phenotype.

Conclusion:
TROP2 expression dynamically changes throughout BTC carcinogenesis, highlighting its complex biological role. High TROP2 correlates with poor patient survival, inflammation, and cancer stem cell-like features. Further studies are required to elucidate the underlying molecular mechanisms.

O7-15-YI
Hypoxia-induced glycolytic shift reflects tumor aggressiveness in liver cancer spheroids

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Background and aims:
Hepatocellular carcinoma (HCC) is marked by substantial biological heterogeneity. Tumor hypoxia reprograms metabolism, shifting energy production toward glycolysis to sustain cells' growth and survival. We investigated how hypoxia-induced metabolic and energetic alterations relate to tumor aggressiveness using HCC models with different degrees of differentiation and malignancy.

Method:
We employed three-dimensional spheroid models derived from 2 immortalized (HepG2 and Hep3B) and 2 primary (HLC21 and HLC19) HCC cell lines. Spheroids were exposed to hypoxic condition (1% O_2) for 48 hrs. Glucose uptake, lactate secretion and ATP production were quantified to assess metabolic adaptation.

Results:
Metabolic adaptations under hypoxia varied across models:

- HepG2 exhibited modest and delayed glycolytic response under both hypoxia and normoxia, with moderate increase in lactate levels, significant under hypoxia only. ATP remained high under normoxia, reflecting efficient oxidative phosphorylation, but decreased under hypoxia, indicating limited glycolytic compensation.
- Hep3B showed a glycolytic phenotype even at baseline with minimal further adaptation to hypoxia. ATP levels remained relatively high under normoxia, consistent with a constitutive glycolytic (Warburg-like) metabolism, indicating low metabolic flexibility.
- HLC21 displayed a strong but delayed increase in lactate secretion, consistent with an adaptive glycolysis typical of less aggressive tumours. ATP showed delayed glycolytic activation under hypoxia, indicating delayed metabolic adaptation.
- HLC19 demonstrated constitutive glycolysis with high lactate levels even under normoxia, indicative of a Warburg phenotype and intrinsic aggressiveness. High ATP was maintained regardless of oxygen, consistent with the Warburg phenotype.

Conclusion:
HCC spheroids adapt to hypoxia through enhanced glycolysis, but the extent of this metabolic shift varies by tumor aggressiveness and cell origin. HLC19-derived spheroids closely recapitulate the metabolic behaviour of aggressive tumours, whereas HLC21 represents a more indolent phenotype. Compared to immortalized lines, primary patient-derived spheroids more accurately reflect *in vivo* tumor responses to hypoxic stress. These findings highlight the value of physiologically relevant models to study metabolic plasticity and inform therapeutic strategies targeting tumor metabolism in HCC.
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PO7-16-YI
Involvement of the ERG1 potassium channel in cholangiocarcinoma cell biology

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Background and aims:
Background and Aim: hERG1 is a voltage-gated potassium channel normally found in excitable cells, but it is often overexpressed in tumors, where it interacts with β1 integrin and activates cancer-related pathways. Intrahepatic cholangiocarcinoma (iCCA) is an aggressive liver malignancy with limited treatment options. This study aimed to investigate the role of hERG1 and its downstream signaling in iCCA biology.

Method:
hERG1 expression was assessed in three iCCA cell lines, and functional studies were performed using siRNA-mediated silencing (si hERG1) and pharmacological inhibition. Cellular behavior was evaluated through standard assays, and molecular and structural changes were analyzed using qRT-PCR, Western blotting, electron microscopy, and transcriptomics.

Results:
hERG1 silencing led to a 75–80% reduction in mRNA and protein expression but did not impact proliferation or viability. In contrast, both genetic silencing and pharmacological inhibition significantly reduced cell motility and impaired angiogenesis, as shown by reduced tube formation in HUVECs exposed to si hERG CCA conditioned media. Gene expression analyses revealed downregulation of epithelial mesenchymal transtion (EMT) and angiogenesis markers. Key oncogenic pathways, including FAK, PI3K, and AKT, were notably suppressed. Ultrastructural analysis showed endoplasmic reticulum swelling and increased vesicular traffic, indicating cellular stress and altered membrane turnover. Transcriptomic profiling confirmed dysregulation in vesicle trafficking and exocytosis, highlithing a broader impact of hERG1 on intracellular dynamics.

Conclusion:
hERG1 plays a critical role in supporting motility and angiogenic potential in iCCA cells without affecting proliferation. Its inhibition alters key oncogenic and cellular processes, positioning hERG1 as a promising therapeutic target in iCCA.

PO8-8
Cyclin M1, a novel therapeutic target for Hepatocellular Carcinoma

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Background and aims:
Hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer and the second cause of cancer mortality. In the USA, the prognosis has an overall 5-years survival of approximately 14%. It has been described that a decrease of magnesium (Mg^{2+}) levels, known as hypomagnesemia, is associated with the progression and metastasis of HCC. This dysregulation worsens the prognosis of the disease; however, the underlying mechanisms remain poorly understood. In this study, we investigated the role of Mg^{2+} in HCC and more specifically, the involvement of the Mg^{2+} transporter CNNM1 in the epithelial-mesenchymal transition (EMT) in HCC, with the aim of identifying a potential therapeutic target

Method:
CNNM1 mRNA expression levels were measured in a cohort of patients with HCC by Ualcan. We performed an *in silico* analysis of CNNM1 expression levels by cbioportal website in 450 patients.
In the *in vitro* studies, SNU 449 cells were silenced CNNM1 and HUH7 cells were overexpressed CNNM1. Cell proliferation, migration, invasion, mitochondrial function and glycosylations were further evaluated.

Results:
We observed an upregulation of CNNM1 mRNA expression levels in a cohort of patients with HCC by Ualcan database. Moreover, an *in-silico* analysis by Cbioportal revealed an increase of CNNM1 levels in patients with tumors in T3 stage compared to T1 stage. In the *in-vitro* studies, we also observed an upregulation of CNNM1 protein levels in mesenchymal cell lines such as SNU 449, SNU 423 and SNU 475 compared to epithelial cells such as HUH7, PLC and HEPG2, suggesting that CNNM1 expression is involved in EMT transition. Thus, we propose to silence CNNM1 in SNU449 cell line and overexpressed CNNM1 in HUH7 epithelial cell line. Silencing *CNNM1* reduces the proliferative and migratory capacity of cells whereas overexpression CNNM1 leads to more mesenchymal phenotype. Importantly, it has been reported that abnormally glycosylated proteins play a role in controlling the aggressive nature of cancer cells, affecting the transformation between epithelial and mesenchymal phenotypes through several mechanisms. To further confirm this finding, we performed glycosylation arrays in cell lines in presence and in absence of CNNM1, observing changes in the sialic acid. Silencing *CNNM1* reduced glycosylations compared to control and overexpressing CNNM1 increased sialic acid glycosylation.

Conclusion:
CNNM1 glycosylation may be a crucial factor in the EMT of HCC through modulating Mg^{2+} metabolism.

PO8-11
Metagenomic profiling of gut microbiome signatures across liver disease stages and HCV-Related hepatocellular carcinoma in Egyptian Patients

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Background and aims:
Dysbiosis in the gut microbiome, particularly concerning the synchronous cross-talk between the gut and the liver, has been associated with various diseases. This study examines the gut microbiome's role in liver diseases among Egyptian patients, with a focus on the hepatitis C virus (HCV) and hepatocellular carcinoma (HCC), both of which are highly prevalent in Egypt.

Method:
Utilizing shotgun metagenomic sequencing, we analyzed microbial gene catalogs and taxonomic profiles from 46 Egyptian patients categorized into five groups: healthy individuals, liver disease patients of different etiologies, post-HCV, treated HCV, and HCV-HCC patients.

Results:
The results revealed that healthy and treated HCV patients exhibited distinct microbial profiles characterized by an abundance of beneficial bacteria, Faecalibacterium and Bifidobacterium ($p < 0.05$), associated with anti-inflammatory short-chain fatty acid production. Conversely, liver disease and HCC patients displayed increased pathogenic bacteria, Escherichia ($p < 0.05$), and genes linked to inflammation and oncogenesis, including lipopolysaccharide biosynthesis.

Conclusion:
These findings suggest a dominance of Faecalibacterium in healthy Egyptians, likely attributable to fiber-rich diets, and cytochrome P450 genes as potential HCC biomarkers, possibly connected to aflatoxin exposure. Treated HCV patients showed significant microbiome recovery, reflecting effective antiviral therapy. These findings emphasize that Egypt-specific factors, such as persistent resistance genes post-HCV due to antibiotic use and the prominence of bile acid metabolism genes, are influenced by high HCV prevalence and environmental exposures like aflatoxins. These dynamics establish a new agenda for regional microbiome studies and provide a detailed perspective on the broader picture.

PO8-12-YI
Reprogramming of tumour-associated macrophages in liver affected by colorectal cancer metastases

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Background and aims:
The development of liver metastases occurs in nearly half of colorectal cancer (CRC) patients and drastically worsens their prognosis. The tumour microenvironment (TME), especially the tolerogenic hepatic niche, plays a critical role in tumour progression and response to therapy. Among immune cells, tumour-associated macrophages (TAMs) are the most abundant and exhibit high plasticity, adopting either pro-inflammatory or immunosuppressive phenotypes depending on environmental factors. Our aim was to characterize the TAMs present in CRC liver metastases (CRLM), to identify their clinical relevance and to explore their potential use as targets.

Method:
TAMs in CRLM were identified in FFPE sections of CRC patients by immunohistochemistry. Additionally, TAMs were isolated from fresh peritumoral tissue samples and sorted by flow cytometry for transcriptional and metabolic profiling. Macrophages differentiated from monocytes were used as in vitro models for drug testing, grown in the presence or absence of medium from primary tumour cells obtained from CRLM specimens. Gene expression was analysed by RT-qPCR while protein expression and localization were determined by immunofluorescence and confocal microscopy.

Results:
The association of TAM morphology in the peritumoral liver with prognosis was further validated in an independent cohort. Larger TAMs, whose presence correlated with poorer survival rates, exhibited an immunosuppressive (M2-like) phenotype, whereas smaller TAMs displayed inflammatory (M1-like) features. These phenotypes are cued and influenced by the cytokines released by tumour cells, as culturing TAMs with different tumour surnatants enabled us to faithfully reproduce the morphological and functional traits observed in TAMs from patient samples. Moreover, the metabolic profiling revealed that large TAMs had elevated riboflavin levels, linked to increased activity of lysine-specific demethylase 1 (LSD1), an epigenetic enzyme influencing their phenotype and morphology. Thus, targeting LSD1 in vitro with inhibitors partially reprogrammed TAM populations towards a more inflammatory and immunostimulatory phenotype.

Conclusion:
TAMs in CRLM exhibit immunosuppressive features that correlate with poor prognosis, and their morphology reflects functional states relevant for patient outcomes. TAM reprogramming by LSD1 targeting represents a promising strategy to enhance anti-tumour immunity in CRLM and improve immunotherapeutic outcomes.

PO9-5-YI
Targeting AKT1, MAPK1, and TP53: A Computational modeling approach to identify novel therapeutic strategies for liver cancer

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Background and aims:
Liver cancer remains a major global health burden driven by complex genetic alterations and dysregulated signaling cascades that promote tumor initiation and progression. Aberrant activation of key oncogenic pathways, including phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated protein kinase (MAPK), and tumor protein p53 (TP53), plays critical roles in hepatocarcinogenesis, yet their integrated molecular interactions remain poorly defined. This study applied computational modeling and bioinformatics analysis of genomic and transcriptomic data to construct liver cancer pathway networks and identify novel therapeutic targets

Method:
Genomic and transcriptomic datasets from 50 liver cancer patients were obtained from The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC). Whole-exome and RNA sequencing data underwent quality control and normalization before downstream analyses. Differentially expressed genes between tumor and normal tissues were identified using DESeq2, and pathway enrichment was assessed through Reactome and KEGG databases. Gene interaction networks were visualized in Cytoscape, while Boolean logic and dynamic modeling were used to simulate pathway interactions and predict therapeutic targets. Validation was performed using clinical and molecular data from an independent cohort of 20 liver cancer patients treated at one of the University Teaching Hospital Biobank in Nigeria under approved ethical protocols.

Results:
Integrative analysis revealed significant dysregulation of multiple pathways: PI3K/AKT showed strong enrichment ($p < 0.01$, fold enrichment > 2), and MAPK/ERK demonstrated high network connectivity (node degree > 5, betweenness centrality > 0.5). Network modeling identified AKT1, MAPK1, and TP53 as key molecular hubs correlating with patient survival and treatment outcomes. Validation confirmed their association with disease progression and therapeutic response, supporting their potential as actionable biomarkers.

Conclusion:
This study used advanced computational modeling to analyze genomic and transcriptomic data from liver cancer patients and identified AKT1, MAPK1, and TP53 as key molecular targets. The findings enhance understanding of how disrupted signaling pathways drive liver cancer and provide a foundation for developing new, more precise therapeutic strategies for improved patient outcomes.

Key Words:*Liver Cancer, Computational Modeling, Bioinformatics, Therapeutic Targets, Signaling Pathways

PO9-7
Characterization of primary biliary cholangitis symptoms and liver transcriptome in aged Mcpip1fl/flAlbCre mice

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Background and aims:
Mcpip1fl/flAlbCre mice, characterized by the Zc3h12a gene (encoding Mcpip1 protein) deleted in liver epithelial cells, exhibit typical primary biliary cholangitis (PBC) symptoms. Already at the age of 6 weeks, mice are characterized by increased levels of antimitochondrial and antinuclear antibodies, elevated total bile acids, and intrahepatic bile duct hyperplasia, disruption of bile duct epithelium and fibrosis. Since PBC is a risk factor for cholangiocarcinoma development we decided to analyse transcriptional changes in livers of 52-week-old control (Mcpip1fl/fl) and knockout (Mcpip1fl/flAlbCre) mice.

Method:
52-week-old Mcpip1fl/fl and Mcpip1fl/flAlbCre male mice were used in this study. Collected material was analyzed by histological stainings (H&E, PSR), qPCRs and next generation sequencing (NGS) of total RNA from livers.

Results:
Histological analysis of 52-week-old Mcpip1fl/flAlbCre mice demonstrated an extensive proliferation of cholangiocytes in the liver parenchyma and portal areas. Cholangiocytes dysplasia was accompanied by bile duct epithelium disruption and fibrosis, resulting in lumen obstruction and bile duct destruction. Mcpip1fl/flAlbCre mice showed increased leukocytes, predominantly T lymphocytes and macrophages, infiltration into the liver parenchyma in comparison to Mcpip1fl/fl controls. NGS analysis revealed 651 differentially expressed genes between Mcpip1fl/flAlbCre and Mcpip1fl/fl mice. 509 were up and 142 were down regulated in knockout animals in comparison to controls. Upregulated genes were annotated to biological processes involved in extracellular matrix biosynthesis (e.g., extracellular matrix and collagen fibril organization, cell adhesion, cell-matrix adhesion, extracellular fibril organization), inflammation (e.g., inflammatory response, immune response, chemotaxis), cell migration and proliferation. Downregulated genes were related to lipid metabolism (e.g., lipid metabolic processes, fatty acid (FA) β-oxidation, FA and cholesterol metabolic processes, FA transport, negative regulation of lipid storage), oxidation-reduction process and canalicular bile acid transport.

Conclusion:
Aged Mcpip1fl/flAlbCre mice are characterized by significant features of PBC, that may further lead to CCA development.

PO9-8-YI

Deep transfer learning-based discovery and validation of latent transforming growth factor binding protein 1 as a prognostic and druggable target in hepatocellular carcinoma

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Background and aims:
Hepatocellular carcinoma (HCC) is a major cause of mortality globally, and current biomarkers such as alpha-fetoprotein show limited diagnostic accuracy, particularly in early stages, underlying the need for improved molecular targets. Latent transforming growth factor ß (TGF-ß) binding protein 1 (LTBP1), a regulator of TGF-β signaling and extracellular matrix remodeling, was investigated for its prognostic and therapeutic potential in HCC.

Method:
In silico analyses using GEPIA, UALCAN, TIMER, and Human Protein Atlas were conducted to evaluate LTBP1 expression, prognostic value, clinical relevance, and immune infiltration in HCC. To identify novel LTBP1 inhibitors, an ensemble of five pre-trained, graph-based deep learning models was fine-tuned using a curated dataset of 47 known LTBP1 modulators from the literature. The resulting ensemble was subsequently validated for predictive performance. This validated ensemble was then used for a virtual screening against a library of 5,767 compounds. The compound library was systematically refined from the ChEMBL database using physicochemical and structural filters, followed by batch molecular docking using AutoDock Vina to validate ligand-protein interactions.

Results:
High LTBP1 expression was linked to poorer survival, advanced pathological stage, and female gender, with the highest levels in Caucasians. LTBP1-correlated genes were enriched in TGF-ß signaling, ECM organization, angiogenesis, immune modulation, hypoxia, and post-translational modifications. In the normal liver, LTBP1 was highest in PBMCs, basophils, neutrophils, smooth muscle cells, fibroblasts, and endothelial cells, and lower in eosinophils, dendritic cells, and monocytes. LTBP1 positively correlated with CAFs, monocytes, macrophages, and neutrophils, and negatively with CD8+ T cells, suggesting a role in ECM remodeling and tumor progression in HCC. The virtual screening employed a robust consensus protocol that required a prediction score greater than 0.9 across all five models to minimize false positives. This approach successfully identified 60 high-confidence candidate molecules. These novel hit compounds are then used for subsequent validation to confirm their potential LTBP1 inhibitory activity. Furthermore, AutoDock Vina confirmed Hypericin and Odm-207 as potential LTBP1-targeting drugs.

Conclusion:
High LTBP1 expression highlights its prognostic value in HCC and its role in tumor-immune interactions, with Hypericin and Odm-207 emerging as promising drug candidates.

PO9-9
Association of the glucagon-like peptide 1 receptor with poor histological grading and metastatic potential of extrahepatic cholangiocarcinoma

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Background and aims:
Our previous report showed that high expression of the glucagon-like peptide 1 receptor (GLP1R) was associated with poor histological grading of intrahepatic cholangiocarcinoma (iCCA), while treatment with GLP1R agonists exerted anti-metastatic potential in iCCA cells, partly by inhibiting GLP1R expression. Since cholangiocarcinoma is highly heterogeneous, the present study aimed to investigate the roles of GLP1R in the progression of extrahepatic cholangiocarcinoma (eCCA).

Method:
Expression of GLP1R in eCCA tissues from patients was investigated using immunohistochemistry. The association with clinicopathological characteristics was analyzed using univariate and multivariable Cox regression analyses. Functional roles of GLP1R in eCCA cells were examined by silencing its expression using siRNA in the eCCA cell line.

Results:
High expression of GLP1R in eCCA tissues was significantly associated with tumor mucin production and poor histological grading ($p < 0.05$). Silencing GLP1R expression showed no effects on the proliferation of KKU-100, an eCCA (perihilar subtype) cell line. However, suppressing GLP1R expression in KKU-100 significantly reduced the migration and invasion of eCCA cells in vitro by inhibiting STAT3 and Akt signaling, resulting in inhibition of epithelial-mesenchymal transition.

Conclusion:
The present findings confirmed the roles of GLP1R in promoting the metastatic potential of eCCA cells. Intervention targeting GLP1R might be helpful for CCA treatment both iCCA and eCCA subtypes.

POSTER ABSTRACT PRESENTATIONS

Clinical Science

PT-1
Outcomes by prior locoregional therapy use from the Phase 3 HIMALAYA study of tremelimumab + durvalumab in unresectable hepatocellular carcinoma

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Background and aims:
In the Phase 3 HIMALAYA study (NCT03298451), STRIDE (Single Tremelimumab [T] Regular Interval Durvalumab [D]) significantly improved overall survival (OS) vs sorafenib (S) in participants (pts) with unresectable hepatocellular carcinoma (uHCC) over a 5-yr follow-up period (hazard ratio [HR], 0.76 [95% confidence interval (CI), 0.65–0.89]; 60-month OS rates: 19.6 vs 9.4%). Locoregional therapy (LRT) is standard of care for patients with embolisation-eligible, liver-confined uHCC; its use before systemic therapy may indicate better prognosis. We report efficacy and safety outcomes in pts with and without prior LRT before enrolment in HIMALAYA.

Method:
Pts were randomised to STRIDE, D monotherapy, or S. In this exploratory *post hoc* analysis, pts were identified by use of any LRT prior to enrolment (TACE, TARE, TAE, SBRT/EBRT, HAIC/TAIC). Baseline characteristics, efficacy and safety were assessed by prior LRT use. OS and serious adverse events (SAEs) were assessed after 5 yrs of follow-up (data cutoff: 1 Mar 2024).

Results:
Overall, 438/1171 (37.4%) pts received prior LRT, including 156/393 (39.7%) treated with STRIDE, 139/389 (35.7%) with D, and 143/389 (36.8%) with S. Baseline characteristics were balanced across treatment arms within LRT subgroups. Across all arms, more pts were recruited from Asian countries (except Japan) among pts with vs without prior LRT (51.4 vs 34.7%), and more had Hepatitis B virus (41.6 vs 24.3%). Pts with prior LRT were enriched in favourable baseline prognostic features compared to pts without prior LRT. A lower proportion of pts with vs without prior LRT had microvascular invasion (20.1 vs 28.5%), ECOG performance status >0 (32.9 vs 40.5%) and BCLC score C (71.2 vs 86.8%). OS HR (95% CI) for STRIDE vs S was 0.69 (0.54–0.89) with prior LRT and 0.80 (0.66–0.98) without prior LRT; 60-month OS rates for STRIDE vs S was 19.7 vs 6.8% with prior LRT and 19.6 vs 11.1% without prior LRT. ORR for STRIDE vs S was 17.9 vs 2.8% with prior LRT and 21.5 vs 6.5% without prior LRT. Treatment-related SAE frequency on STRIDE was 16.8% with prior LRT and 18.0% without prior LRT, similar to the overall cohort (17.5%).

Conclusion:
In this *post hoc* analysis, STRIDE sustained its OS benefit over S for pts with and without prior LRT use, similar to findings in the overall cohort, with no new safety concerns. These results demonstrate a favourable risk-benefit profile for STRIDE vs S in pts with uHCC, regardless of prior LRT use.

PT-2
Serum Procalcitonin: A new tumor biomarker for the diagnosis and monitoring of fibrolamellar hepatocellular carcinoma

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Background and aims:
Fibrolamellar carcinoma (FLC) is a rare primary liver cancer that develops in non-cirrhotic livers, typically affecting young patients who usually present with normal levels of known serum tumor biomarkers. The observation of markedly elevated serum procalcitonin (PCT) in one patient led us to investigate the potential role of PCT as a biomarker in a larger cohort of FLC cases.

Method:
Serum PCT concentrations were measured in 34 samples from 18 patients with metastatic FLC, as well as in 64 patients with hepatocellular carcinoma (HCC), 24 with cholangiocarcinoma (CCA), and 20 patients with cirrhosis without HCC, from both European and U.S. cohorts. Using RNA sequencing, we analyzed the expression of the CALCA gene, which encodes PCT, in 27 FLCs, 331 HCCs, 39 CCAs, 71 hepatoblastomas, 34 hepatocellular adenomas, and 55 non-tumoral liver samples. Spatial transcriptomic analysis was performed on three FLCs, and PCT immunohistochemistry was conducted on 13 FLCs and 34 other primary or secondary liver cancers.

Results:
The median serum PCT level was significantly elevated in 8 FLC patients (55.2 µg/L) compared with HCC (0.14 µg/L), CCA (0.16 µg/L), and cirrhosis (0.11 µg/L; P = 0.0005) in the European cohort. These findings were independently validated in a U.S. cohort of 10 FLC patients compared with HCC and CCA cases (P = 0.0002). Across cohorts, elevated serum PCT was observed in 83% of FLC cases versus only 3% of HCC and CCA patients (P < 0.0001).In four patients followed longitudinally, PCT levels correlated with radiological response, stability, or progression according to RECIST 1.1 criteria. For example, serum PCT increased from 51 µg/L (102× the upper limit of normal) to 581 µg/L (1,162× ULN) following tumor progression under immunotherapy.
RNA sequencing revealed significant CALCA overexpression in FLC compared to other primary liver tumors (P < 0.0001), with an AUC of 0.975 versus CCA, and 0.994 versus HCC, demonstrating excellent diagnostic sensitivity and specificity for this rare liver cancer. Spatial transcriptomics localized CALCA expression specifically to tumor cells harboring the DNAJB1-PRKACA fusion gene. Immunohistochemistry confirmed PCT overexpression in tumor cells in 77% of FLCs, but not in other primary or secondary liver cancers (P < 0.0001).

Conclusion:
Procalcitonin is a sensitive and specific biomarker for fibrolamellar hepatocellular carcinoma, both in serum and tumor tissue, with potential clinical utility for diagnosis and monitoring of treatment response.

PT-3-YI

Outcomes of cisplatin, gemcitabine, and durvalumab according to TOPAZ-1 study eligibility: a large global analysis in a real-world setting

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Background and aims:
Cisplatin (C), gemcitabine (G), plus durvalumab (D) have emerged as a new first-line standard of care for unresectable biliary tract cancer (BTC). This international multi-center study aimed to assess the efficacy and tolerability of CGD in routine clinical practice, comparing outcomes between patients within and outside key eligibility criteria for the TOPAZ-1 trial.

Method:
The study cohort consisted of patients with biliary tract cancer treated with CGD in the first-line setting. Patients were divided into TOPAZ-1-in (meeting all the eligibility criteria) and TOPAZ-1-out (meeting at least one exclusion criteria). The primary objectives were overall survival (OS) and progression-free survival (PFS), with objective response rate (ORR), disease control rate (DCR), and safety as secondary endpoints.

Results:
1358 patients from 53 sites across 12 countries in the USA, Asia, and Europe were enrolled in the study. After a median follow-up of 14.5 months (95%CI: 13.7-36.5), estimated median OS (mOS) was 15.5 months and median PFS (mPFS) 7.6 months. In the TOPAZ-1-in group (912 patients), mOS was 16.1 months, while in the TOPAZ-1-out group (446 patients) mOS was 12.5 months (HR 0.69, p=0.0001). mPFS was 8.2 months in the TOPAZ-1-in group and 6.5 months in the TOPAZ-1-out group (HR 0.73, p<0.0001). Among TOPAZ-out patients, only active infection, elevated bilirubin, and ECOG > 1 were linked to poorer OS, while no detrimental impact emerged for ALT/AST abnormalities, corticosteroid use, renal or hematologic parameters, or prior surgery within 6 months, suggesting treatment effectiveness was broadly maintained across clinical subgroups. Furthermore, TOPAZ-1-out patients experienced no significant increase in adverse events compared with the TOPAZ-1-in group, confirming that treatment safety was consistently maintained across both populations.

Conclusion:
Real-world data indicate that CGD maintains consistent effectiveness even among patients in the TOPAZ-1 out group, whose overall survival was comparable to that observed in the phase III trial. Moreover, TOPAZ-out patients did not experience higher toxicity, supporting the use of the regimen in clinical practice

PT-4

JAKaL: Phase Ib study of itacitinib, a selective JAK1 inhibitor, for the management of advanced stage hepatocellular cancer after failure of first line therapy

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Background and aims:
Hepatocellular carcinoma (HCC) develops on background chronic liver disease where uncontrolled inflammation drives hepatocarcinogenesis. First-line therapies have limited response. There are no agents that specifically target the underlying liver inflammation. We investigated the safety and efficacy of itacitinib, a highly selective JAK1 inhibitor, as a potential second- or third-line therapy. Biomarkers of response were investigated.

Method:
Participants with advanced stage HCC, Child Pugh ≤B7 who had progressed through at least one previous line of therapy received 400mg of itacitinib QID every 28 days. Treatment-related adverse events (trAEs) were assessed weekly during cycle 1 then every 28 days (CTC-AE version 4.03). Response was assessed 8-weekly using RECIST 1.1. Progression-free (PFS) and overall survival (OS) were reported as secondary endpoints. Tumour samples were analysed for targeted transcriptomics. Sequential serum samples were assessed for metabonomic determinants of toxicity and response.

Results:
19 patients were enrolled in the study. The most common trAEs were thrombocytopenia (31%), fatigue (26%) and palmar-plantar erythrodysesthesia syndrome (26%); four episodes of dose-limiting thrombocytopaenia were observed. Over a median follow-up of 3.5 months, the best overall response was stable disease (47%). Median PFS and OS were 3.5 (95% CI: 2.6 - 4.5 months) and 7.4 months (95% CI: 4.3-10.5 months), respectively. Subgroup analysis illustrated a significantly increased risk of progression for patients that had received combination immunotherapy prior to itacitinib (HR 4.7, 95%CI 1.3-16.6, *p*=0.016). Untargeted tumour and serum transcriptomics identified a signature predictive of response.

Conclusion:
Itacitinib either as second- or third-line therapy showed promising activity. We identified a transcriptomic signature predictive of response.

PO1-02-YI
Pathologic versus radiologic response to neoadjuvant immunotherapy in hepatocellular carcinoma: results from the NeoHCC international consortium

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Background and aims:
Immune checkpoint inhibitors (ICI) administered before liver resection (LR) induce tumour regression in hepatocellular carcinoma (HCC). However, the quantitative relationship between radiologic (Rad) vs pathologic (Path) response is poorly understood.

Method:
The NeoHCC consortium pooled individual-level data from 146 patients (pts) with HCC receiving ICI before LR as part of 7 phase I–II or observational studies conducted in 14 international centres. Rad response was assessed by RECIST v1.1 (n=146) and modified RECIST (mRECIST, n=95). Path complete (pCR) and major responses (MPR) were defined as 100% and ≥90% tumour necrosis, respectively. Rad-Path correlations were evaluated using Pearson score, linear regression, LASSO penalised variable selection, and generalised additive models (GAM) with penalised splines.

Results:
Pts received preoperative ICI between Aug 2017 and Feb 2025. They were predominantly male (78%), most with viral aetiology (64%) and early/intermediate BCLC stage (61%). Seventy-three percent had a single nodule, with a mean dominant tumour diameter of 6.8 cm. Combination ICI was administered in 70% of cases. Path responses occurred in 15.8% (pCR) and 24.0% (MPR), while Rad objective responses were observed in 25% (RECIST) and 30% (mRECIST). Rad response correlated with Path response ($r=-0.71$, $R^2=0.51$, $p<0.001$), with linear regression demonstrating an 11%-point increase in necrosis/fibrosis per 10% diameter reduction ($\beta=-1.11$, $p<0.001$). However, GAM revealed a non-linear relationship for the pCR probability ($edf=1.96$, $\chi^2=25.4$, $p<0.001$), with the steepest increase in pCR probability between –20% and –40% Rad reduction.
Discordant RECIST/mRECIST classification was observed in 9.5% of cases. Pts achieving an objective response by mRECIST but not RECIST (RECIST–/mRECIST+, n=6, 6.3%) achieved MPR in 50%, while those with RECIST+/mRECIST– pattern (n=3, 3.2%) also showed substantial Path regression (pCR 33%, MPR 33%). These findings indicate that RECIST and mRECIST capture complementary aspects of ICI-induced regression. Lastly, LASSO regression confirmed Rad response dominance over baseline clinical variables for Path prediction (AUC 0.93 for pCR, 0.92 for MPR versus 0.50 for baseline-only models).

Conclusion:
Rad response demonstrates significant correlation with Path regression in neoadjuvant ICI-treated HCC. RECIST and mRECIST capture complementary information, and integration of both criteria optimises response evaluation and should inform future trial endpoint selection.

PO1-03-YI
The IL-7 rs16906115 single nucleotide polymorphism alters the risk for the development of treatment-related AEs in patients with HCC treated with immunotherapy

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Background and aims:
The interleukin-7 (IL7) rs16906115 single nucleotide polymorphism (SNP) alters B cell-specific IL7 expression. In immune-checkpoint-inhibitor (ICI) treated patients with melanoma, carriers of the minor allele were at increased risk of treatment-related adverse events (trAEs). The importance of this SNP in patients with hepatocellular carcinoma (HCC) undergoing systemic treatment is unknown.

Method:
We included HCC patients treated with systemic therapies at three institutions (Vienna/Austria, Hamburg-Eppendorf/Germany, Seongnam/Republic of Korea). SNP-genotyping was performed using real-time PCR systems following the manufacturer's recommendations.

Results:
We included 345 patients (male: n=283, 82.0%) with a median age of 64.1 (IQR: 56.9-71.9) years mainly undergoing atezolizumab/bevacizumab treatment (95.7%). Observed allele frequencies (wild-type/heterozygous/homozygous variants) were: G/G: 60.0% / G/C: 33.0% / C/C: 7.0%.
When applying a time-dependent approach to account for treatment-exposure, we found a stepwise increase of the risk of trAE development linked to IL-7 genotype (C/C or C/G vs G/G, hazard ratio [HR]: 1.33 [95% confidence interval (CI): 1.03-1.72], p=0.027). In total, 19/24 patients (79%) harbouring two minor alleles (C/C) developed trAEs (% grade 1/2/3: 50%/21%/8%) and treatment was stopped due to trAEs in 8%. Analysis of lymphocyte stability over time (baseline vs. day 21 during treatment) did not reveal significant differences in immune cell counts depending on IL7 genotype.
Ultimately, patients harbouring the C/C genotype tended to have a worse median overall survival compared to patients harbouring at least one wild-type allele (10.3 [95%CI: 6.7-18.8] vs 16.2 [95%CI: 12.6-18.8] months; p=0.241).

Conclusion:
The IL-7 rs16906115 genotype may help to predict the risk for trAE development and therefore for the selection of patients appropriate for treatment regimen with a higher or lower risk of trAEs.

PO1-10-YI

Prognostic stratification of patients with biliary tract cancer treated with chemoimmunotherapy

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Background and aims:
Prognostic models have been developed to assist clinicians in stratifying patients with biliary tract cancer (BTC) into distinct risk categories. The objective is to explore and validate a novel prognostic index for patients treated with first-line cisplatin, gemcitabine and durvalumab (CGD).

Method:
This is a retrospective, multicenter, real-world study including 712 patients in the training cohort and 646 patients in the validation cohort from 12 Eastern and Western countries enrolled between September 2022 and May 2025. Using multivariate analysis for overall survival (OS) and applying the adjustment methods of Holm-Bonferroni, Benjamini-Hochberg, and Hommel, we identified 5 baseline statistically significant variables: disease stage, neutrophils, CEA and CA 19-9 levels, and ECOG PS. According to the hazard ratio (HR) of each variable, β coefficients were calculated and the following formula was applied: (0.1757 * neutrophils value) + (0.5055 * ECOG PS) + (1.4037 * disease stage) + (0.1108 * CA 19-9) + (0.2126 * CEA). According to tertiles, we developed a prognostic model called the SENECA index, dividing the population into three risk groups: low-risk (≤ 2.14), intermediate-risk (2.15 – 2.89), and high-risk (> 2.89).

Results:
Median OS was 23.4 months in low-risk group,16.1 months in intermediate-risk group, and 8.3 months in high-risk group (low-risk HR 0.20, intermediate-risk HR 0.36, high-risk HR 1, p < 0.0001). Median

progression-free survival (PFS) was 11.0 months in low-risk group (33.1%), 8.8 months in intermediate-risk group (33.3%), and 5.5 months in high-risk group (33.5%) (low-risk HR 0.35, intermediate-risk HR 0.55, high-risk HR 1, $p < 0.0001$). There was no difference in overall response rate (low-risk 33.0%, intermediate-risk 35.5%, and high-risk 28.3%; $p = 0.2969$), while the disease control rate was significantly different across the three risk groups (low-risk 80.2%, intermediate-risk 75.4%, and high-risk 61.4%; $p < 0.0001$). The prognostic role in terms of OS and PFS of the SENECA index was confirmed in the validation cohort.

Conclusion:
The SENECA index is a practical instrument for prognostic stratification of patients with BTC receiving CGD.

PO1-12-YI

Prognostic role of adverse events in a worldwide population of patients with biliary tract cancer treated with cisplatin, gemcitabine, and durvalumab or pembrolizumab.

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Background and aims:
Biliary tract cancers (BTC) are aggressive malignancies with limited treatment options. The addition of anti–PD-L1 (durvalumab) or anti–PD-1 (pembrolizumab) to cisplatin–gemcitabine improved overall survival (OS) without a major rise in severe toxicity. Immune-mediated adverse events (imAEs) may indicate enhanced immune activation and correlate with efficacy.

Method:
An international cohort of patients (pts) with locally advanced or metastatic BTC, including intrahepatic, extrahepatic cholangiocarcinoma and gallbladder cancer, was treated with chemoimmunotherapy. Primary endpoints were OS and progression-free survival (PFS), analyzed in relation to both general toxicities and immune-mediated adverse events (imAEs). Variables found to be significant in univariate analyses for OS and PFS were subsequently included in multivariate Cox models.

Results:
1359 pts were enrolled in the study, imAEs occurred in 276 pts (20.3%). At both univariate and multivariate analysis imAEs were associated with improved PFS (HR 0.66, p < 0.0001) and OS (HR 0.71, p = 0.0007). Specifically, hyperthyroidism (PFS HR 0.59, p = 0.03; OS HR 0.35, p = 0.002) and imAEs classified as "other" (musculoskeletal, pulmonary, neurological, cardiac) (PFS HR 0.65, p = 0.000; OS HR 0.47, p = < 0.0001) showed a prognostic impact on PFS and OS at univariate and multivariate analysis. Hypothyroidism was associated with better PFS (HR 0.66, p = 0.009) and remained significantly associated with improved PFS in the multivariate model, while no significant association was observed for OS. Rash was associated with prognostic impact on PFS (HR 0.78, p = 0.03) and OS (HR 0.69, p = 0.007) only at univariate analysis. Concerning general toxicities, patients experiencing decreased appetite (PFS HR 1.42, p < 0.0001; OS HR 1.58, p < 0.0001) and hyponatremia showed worse OS and PFS (PFS HR 1.54, p = 0.0008; OS HR 1.73, p = 0.0003), whereas those with neutropenia (PFS HR 0.78, p < 0.0002; OS HR 0.71, p < 0.0001) exhibited improved OS and PFS at univariate analysis. All three associations were confirmed at multivariate analysis. ALT increase was significantly associated with PFS and OS at univariate analysis (PFS HR 1.22, p = 0.012; OS HR 1.25, p = 0.02), and with PFS (HR 1.17, p = 0.04) only at multivariate analysis.

Conclusion:
The observed association between both imAEs and general toxicities with OS and PFS suggests that these events might serve as potential surrogate markers of treatment benefit.

PO1-13
Optimizing Hepatocellular Carcinoma (HCC) patient Care: Global study unveils best practices in three critical dimensions of multidisciplinary teams (MDTs)

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Background and aims:
MDTs are crucial for improving outcomes for HCC patients, such as increased overall survival. However, low MDT effectiveness can lead to suboptimal care. To examine this, the MDT Aid Program (MAP) maturity framework assesses MDT performance across 6 dimensions: Access to MDT, Process, Technology, Quality Assurance (QA), Capabilities, and Culture. The aim of this study is to identify the dimensions with the greatest global maturity variance and outline best practices in those dimensions.

Method:
Data was collected through 200+ semi-structured interviews and 36 workshops involving 36 leading centers globally. A structured questionnaire evaluated MDT set-up, process, patient prioritization, MDT role in and pathways, and members' qualitative perceptions on outcomes and cost. Responses were mapped to a maturity matrix (S: 1-4). The 3 dimensions with largest variances (VAR) were used to select the best practices associated with the highest MDT maturity. We describe those best practices, and analyse them for implementation in other centres.

Results:
The analysis showed the most substantial disparities in MDT maturity in 3 key dimensions: Access to MDT (VAR=0.51), Technology (VAR=0.38), and QA (VAR=0.63), revealing differences among the involved leading centers. To address this, best practices to improve MDT effectiveness have been identified, selected and described.

Access to MDT: Highest maturity is achieved by enabling virtual participation of doctors in referring regional hospitals, thus ensuring equitable care in underserved regions. MDT coordination and organized patient lists also facilitate comprehensive discussions and a high patient throughput.
Technology: Advances are marked by AI models for improved decision-making and by synchronization of electronic patient records with MDT preparation, ensuring accuracy and reliability of the case information presented.

QA: Key practices include establishing hospital-based, local or national cancer registries, engaging in robust QA certification programs, and establishing regional MDT networks for collective quality improvements.

Conclusion:
This global assessment unveils the most effective and actionable strategies to enhance MDT effectiveness in the areas of highest variability (patient access to MDT, technology, and QA), with an aim to provide actional insights to support MDTs improve. By spotlighting best practices, we provide a blueprint to empower MDTs, address disparities, and improve HCC care for patients worldwide.

PO1-14
Long-term survival and cure fraction in advanced hepatocellular carcinoma under immunotherapy in randomized controlled trials and real-world data

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Background and aims:
Immune checkpoint inhibitors (ICIs) lead to prolonged overall survival and even cancer cure in several tumor types. Mixture cure models (MCMs) allow estimation of long-term survivor fraction and cure fraction but have not yet been applied in HCC.

Method:
We selected positive phase 3 randomized controlled trials of ICI regimens in first-line advanced HCC with mature follow-up (≥30 months) and analyzed a cohort of patients with HCC treated with atezolizumab–bevacizumab. After Kaplan-Meier curves reconstruction, MCMs were used to assess the fraction of long-term survivors using overall survival (OS) and the fraction of cure using progression-free survival (PFS).

Results:
HIMALAYA trial reported median follow-up of 60 months and MCMs estimate long-term survival of 12.8% (95%CI:8.5-18.6%) in durvalumab-tremelimumab versus 5.2% in sorafenib (95%CI:2.6-10.2%); cure fraction was not assessable.In CheckMate9DW (median follow-up: 35.2 month), MCMs estimated a long-term survival of 8.7% (95%CI:0.2–81.3%) versus 4.1% (95%CI:0.1-66.1%) and a cure fraction of 17.8% (95%CI:12.0–25.8%) versus 3.5% (95%CI:0.7–16.7%) for nivolumab-ipilimumab and sorafenib/lenvatinib respectively. The analysis of the IMbrave150 trial was not possible due to the short median follow-up (15.6 months). 1581 patients treated by atezolizumab–bevacizumab were analyzed (median follow-up: 34.7 months). MCM estimated 12.3% (95%CI:9.3-16.1%) of long-term survivors and 7.9% (95%CI:6.3-9.8%) of cure.Radiological response was associated with higher fraction of long-term survival and cure.In 1187 patients meeting the IMbrave150 criteria, MCM estimated 15.4% (95%CI:10.6-18.5%) of long-term survivors and 9.1% (95%CI:7.3-11.4%) of cured fraction.Albumin, bilirubin, and hepatitis C predicted long-term survival and albumin and hepatitis C predicted cure.

Conclusion:
Cure modeling shows that 10–15% of advanced HCC patients treated with ICIs combotherapy achieve long-term survival, with 7–9% of cure fraction.

PO2-1-YI

Non-invasive tests for clinically significant portal hypertension in patients with compensated advanced chronic liver disease and hepatocellular carcinoma

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Background and aims:
The applicability of non-invasive tests (NITs) for clinically significant portal hypertension (CSPH) in patients with hepatocellular carcinoma (HCC) is controversial. We performed a head-to-head comparison of the discriminative ability of various NITs for CSPH and evaluated rule-in/-out criteria in patients with HCC.

Method:
We conducted a retrospective study including 283 patients with HCC undergoing HVPG measurement at the Vienna Hepatic Haemodynamic Lab with available data on NITs (i.e., liver stiffness measurement [LSM], platelet count [PLT], von Willebrand factor antigen [VWF:Ag], and the ratio of VWF:Ag and PLT [VITRO]). For the subsequent analysis, we focused on the main target population for CSPH-NITs, i.e., compensated advanced chronic liver disease (cACLD).

Results:
Among 164 patients with cACLD (mean age 66 years, 86.0% male, 31.1%/32.3%/16.5% alcohol-associated/viral/metabolic dysfunction-associated steatotic liver disease), most were BCLC 0/A (50.6%, B 35.4%, C 14.0%). The CSPH prevalence was 46.3%, the median LSM was 20.0 kPa (IQR: 13.3-37.9), median HVPG was 9 mmHg (IQR: 6-14), and mean VWF:Ag/VITRO were 266±119%/2.30±1.81.
The VITRO score yielded the highest discriminative ability to detect CSPH (AUC 0.834 [95%CI: 0.772-0.896]), followed by ANTICIPATE±NASH (AUC 0.822 [95%CI: 0.756-0.887]), PLT (AUC 0.803 [95%CI: 0.734-0.871]), LSM (AUC 0.779 [95%CI: 0.705-0.852]) and VWF:Ag (AUC 0.707 [95%CI: 0.628-0.785]). The application of the Baveno VII criterium (LSM<15kPa & PLT>150G/L) and the VITRO score (≤1.0) individually showed an excellent performance for ruling out CSPH (sensitivities ≥95%, NPV 100%/87.9%). For ruling in CSPH by individual criteria, the VITRO score provided the highest PPV (≥2.5, specificity/PPV 89.8%/83.0%), followed by the Baveno VII criteria (specificity/PPV 81.8%/74.6%). When sequentially applying Baveno VII criteria and VITRO, the grey zone could be significantly reduced to 32.3% (sensitivity/NPV 94.7%/92.2%; specificity/PPV 73.9%/84.4%).
HCC characteristics did not seem to interfere with CSPH-NITs.

Conclusion:
The discriminative ability in cACLD patients with HCC was comparable to patients without HCC. However, PPVs of established criteria were <90%, which may be explained by the comparatively low prevalence of CSPH in this context.

PO2-2-YI
Cholangiocarcinoma in individuals with chronic liver disease is diagnosed earlier leading to better prognosis

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Background and aims:
Cholangiocarcinoma (CCA) is a lethal cancer with rising incidence and mortality worldwide. Chronic liver disease (CLD) is recognised as an important risk factor, but its impact on tumour presentation and outcomes remains poorly defined. We aimed to compare the clinical course of CCA in patients with and without CLD.

Method:
We retrospectively analysed 3,743 patients diagnosed with CCA between 2010 and 2024 across participating international centres. Patients were classified as CLD (n = 993) if a diagnosis of cirrhosis, primary sclerosing cholangitis (PSC), viral hepatitis, or other chronic liver condition preceded their cancer diagnosis, and non-CLD (n = 2,750) otherwise. Demographic, clinical, biochemical, and outcome data were compared.

Results:
Patients with CLD were more frequently male (67% vs. 53%) and younger (63 vs. 66 years) than non-CLD individuals. They more often presented with intrahepatic tumors (64% vs. 42%), better performance status (ECOG 0: 53% vs. 35%), lower CA19.9 levels (56 vs. 135 U/mL), and earlier stage disease (localized: 57% vs. 43%; metastatic: 23% vs. 31%). Accordingly, curative-intent surgery was more common (60% vs. 48%), resulting in improved median overall survival (mOS: 12.2 vs. 11.1 months, $p < 0.05$) and higher 5-year survival (OR: 1.64, $p < 0.01$), particularly in intrahepatic CCA (mOS: 14.2 *vs.* 11.1 months, $p<0.001$; 5-year survival OR: 2.05, $p<0.001$). Treatment response across modalities did not differ. Within the CLD cohort, prior diagnosis of primary sclerosing cholangitis and cirrhosis were strongly associated with earlier-stage CCA detection.

Conclusion:
Patients with pre-existing CLD are more likely to be diagnosed with CCA at an earlier stage, contributing to improved survival. These findings support evaluation of structured surveillance programs in high-risk CLD populations.

PO2-4-YI
Beyond the Algorithm: Tumor-Board determinants of treatment-stage migration across the BCLC stages (2020–2024)

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Background and aims:
The multidisciplinary tumor board (MTB) is pivotal in tailoring treatment for hepatocellular carcinoma (HCC), particularly when evidence-based first-line options supported by overall survival (OS) data are unsuitable due to patient, technical, or contextual factors, or when multiple treatment options show OS benefit but lack direct comparative evidence. The BCLC algorithm have a key concept central to MTB deliberations: *treatment-stage migration (TSM)*, which allows deviation from linear, stage-based recommendations. Despite their importance, real-world determinants of TSM remain poorly characterized.

Method:
We retrospectively analyzed all cases discussed by the BCLC-MTB between January 2020 and December 2024. Eligible cases involved adult HCC patients presented for treatment decision-making. Data collected included age, BCLC stage, prior therapies, TSM decision, and underlying rationale.

Results:
A total of 800 cases were reviewed by the MTB, 368 were eligible cases (295 patients), 31% (n=114) involved TSM. The median age was 67 years, and 46% were treatment-naïve. TSM was most frequent in BCLC-B (47.3%) and BCLC-A (26.4%) stages. The principal reasons for migration were technical issues (33.3%), untreatable progression (16.7%), and radiological response (10.5%). Comorbidities and/or advanced age influenced 22.8% of TSM decisions, particularly among BCLC-A patients. Patients selected for TSM were older (median 69 vs. 67 years, p=0.036) and more frequently pretreated (66.7%).

Conclusion:
One-third of HCC cases discussed at the MTB required TSM, most commonly driven by technical or patient-related constraints. These findings highlight the central role of multidisciplinary deliberation in individualizing therapy to tailoring the recommendations according to the priorities establish between patients and physicians as well as according to the treatment goal and underscore the need to incorporate TSM rationale into trial design and survival modeling.

PO2-9
Impact of deprivation on HCC patient outcomes at the Royal Free Hospital between 2014-2023

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Background and aims:
HCC mortality rates in the UK have increased three-fold in the last 50 years and are projected to increase further, representing a major public health concern disproportionally affecting marginalised groups. Socioeconomic background and health inequalities may influence the development of chronic liver disease, access to HCC treatment and survival. This study evaluates the relative impact of deprivation on HCC patients receiving treatment at The Royal Free Hospital over a 9-year period.

Method:
The medical records of all HCC patients receiving treatment between 2014-2023 were retrospectively reviewed and data collected on patient characteristics, survival and level of deprivation as defined by the UK Index of Multiple Deprivation (IMD). Levels of deprivation were classified as high (Tertile 1), medium (T2) and low (T3) according to seven key domains. Univariate and multivariate models were constructed to identify clinical and socioeconomic variables correlating with survival (OS).

Results:
A total of 1074 HCC patients were included, 28% in T1, 40% In T2 and 29% in T3. Compared to T3, patients from deprived backgrounds were younger (median age 61 versus 67 years, $p<0.01$), more likely to be of Asian or Black ethnicity ($p<0.001$) and had higher rates of viral chronic liver disease (64.5% versus 32.1%, $p<0.001$). In contrast, rates of MAFLD were highest in least deprived patients (23.6% versus 8.7% $p<0.001$). Route to diagnosis differed, with 49% of T1 patients detected via surveillance versus 34% in T3 ($p<0.001$) and higher rates of incidental and symptomatic diagnosis in T3 (incidental; 25.6% vs 16%, symptomatic; 40% vs 35%). No significant differences were observed in BCLC stage, AFP or presence of portal vein thrombus (PVT). In univariate analysis increased age, advanced stage disease, AFP >400ng/ml, PVT and symptomatic presentation were associated with worse OS. In contrast, median OS was improved in Asian patients compared to White (HR 0.61; 95% CI 0.42-0.88, $p=0.009$) and in patients with higher levels of deprivation compared to those with lower levels (HR 0.79; 95% CI 0.65-0.97 $p=0.02$). After adjusting for confounders using multivariate analysis, only age, BCLC stage and AFP remained significantly associated with survival.

Conclusion:
Levels of socioeconomic deprivation and ethnicity have a significant impact on HCC patient demographics, mode of presentation and overall survival. Targeted public health interventions may improve time to HCC diagnosis and survival outcomes

PO2-10
Temporal trends in survival time of patients with uHCC undergoing TACE: a large cohort and systematic review

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Background and aims:
Transarterial chemoembolization (TACE) is standard for intermediate-stage hepatocellular carcinoma. Despite advances including drug-eluting beads TACE (DEB-TACE), improved catheterization techniques, optimized patient selection, and expanded second-line therapies, their collective impact on real-world overall survival (OS) remains unclear. This study evaluates TACE efficacy trends over the past decade.

Method:
This integrated analysis harmonized data from a large multicenter cohort of 9,111 patients (2010-2019) with a comprehensive systematic review of the literature from 2009-2023, which encompassed 607 studies (682 cohorts, >140,000 patients). Study populations were stratified into predefined subgroups: Ideal and Target, based on liver function (Child-Pugh A-B), performance status (ECOG 0 or 0-1), and disease burden (absence of macrovascular invasion or extrahepatic spread). The impact of DEB-TACE introduction was rigorously assessed using propensity score matching and interrupted time series analysis. Furthermore, we implemented a range of advanced statistical techniques—including inverse probability weighting, Cox regression, machine learning-based correction, and linear regression—to account for potential confounders.

Results:
In the multicenter cohort , no significant improvement in median OS was observed over time after comprehensive adjustment. Subgroup analyses revealed that only Ideal candidates demonstrated significant OS improvement trends. Crucially, DEB-TACE demonstrated no survival advantage over cTACE in propensity score-matched analyses across all subgroups. The systematic review confirmed stagnant OS trends globally (P=0.81), with a significant improving trend exclusively in Japan/South Korea (Slope: 0.871 [0.314-1.428], P=0.009), Western countries (Slope: 1.520 [0.802-2.239], P=0.001), but not in China (Slope: -0.034 [-0.521-0.453], P=0.332). the consistent stagnant trends were observed in subgroup analyses of cTACE vs DEB-TACE, prospective vs retrospective, sample size ≤100 vs >100 patients, and single arm vs non-randomized vs randomized. Geographical disparities linked better outcomes to stricter patient selection, not technique.

Conclusion:
This large integrated analysis reveals stagnant OS after TACE over the past decade despite technical advances. Isolated improvements in Japan/South Korea and Western countries reflect better patient selection, not technological superiority. Precision patient selection appears more impactful than technical modifications alone.

PO2-11-YI
Multimodal artificial intelligence for predicting therapeutic decisions in hepatocellular carcinoma: integrating clinical reports and computed tomography imaging

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Background and aims:
Multidisciplinary management of hepatocellular carcinoma (HCC) requires complex decision-making integrating tumor burden, liver function, and performance status. Although multidisciplinary management can improve outcomes, it is resource-intensive and not universally feasible. We developed a multimodal deep learning framework integrating clinical text reports and computed tomography (CT) imaging to predict therapeutic decisions in HCC patients.

Method:
We retrospectively analyzed 240 unstructured clinical reports with corresponding CT images from 204 patients evaluated at a tertiary referral center between September 2020 and November 2024. Therapeutic decisions were classified into seven categories: liver transplantation, surgical resection, percutaneous ablation, transarterial treatments, systemic therapy, best supportive care, and continued follow-up. A multimodal architecture combining BioBERT for clinical text analysis with a convolutional neural network for CT image feature extraction was developed. The model was trained using an 80:20 split and evaluated using accuracy, sensitivity, specificity, precision, F1-score, and balanced accuracy.

Results:
The cohort included 204 patients (mean age 71.6±10.3 years, 71.2% male). Therapeutic decisions comprised transplantation (8%), resection (7%), ablation (7%), transarterial treatments (9%), systemic therapy (28%), best supportive care (22%), and follow-up (19%). The multimodal model achieved 95.5% overall accuracy, 95.0% sensitivity, 94.0% precision, 94.4% F1-score, 95.0% balanced accuracy, and 84.7% specificity in replicating expert clinical decisions. The confusion matrix demonstrated excellent discrimination across all therapeutic classes, with minimal misclassification between treatment categories.

Conclusion:
A multimodal artificial intelligence framework integrating unstructured clinical reports and radiological imaging accurately predicts therapeutic decisions in HCC with performance exceeding 95%. While requiring prospective validation and interpretability enhancement, this approach demonstrates potential as a clinical decision support tool to standardize care, optimize multidisciplinary team workflows, and support evidence-based treatment selection in HCC management.

PO2-12-YI
Exploring the impact of mitochondrial biomarkers on HCC risk according to etiologic drivers: a multicenter study

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Background and aims:
Metabolic dysfunction-associated steatotic liver disease (MASLD) overcame HCV and alcohol-related hepatitis (ALD), becoming the main cause of hepatocellular carcinoma (HCC). We recently showed that circulating mitochondrial (mt-) biomarkers (*D-loop*, ccf-COXIII) increase in MASLD patients and accurately predict HCC risk. However, it remains to elucidate whether these biomarkers are MASLD-specific. We aim to: (1) assess *D-loop* and ccf-COXIII levels in a multicenter cohort of 1231 HCV, ALD and MASLD patients of whom 332 with HCC; (2) develop new models for HCC diagnosis employing mt-biomarkers and compare them with standard scores (aMAP, Fib4, APRI, Forn's index, Fibro-alpha).

Method:
D-loop and ccf-COXIII were measured by qRT-PCR. Their levels were compared across either etiologies or within each etiology group (MASLD vs MASLD-HCC; ALD vs ALD-HCC; HCV vs HCV-HCC). Multivariate analyses were adjusted for age, gender, BMI, diabetes (T2DM) and presence of cirrhosis. Random forest (RF) analysis, a machine learning method, was exploited to build-up new diagnostic tools.

Results:
MASLD-HCC subjects had higher BMI, T2DM rate and serum lipids compared to HCC from other etiologies ($p<0.01$). In this subgroup, the mean size of primary nodules was larger than ALD-HCCs or HCV-HCC patients, as well as a greater number of non-cirrhotic MASLD-HCC cases were recorded ($p<0.05$). *D-loop* levels raised in MASLD-HCC patients compared to MASLD ones regardless of cirrhosis and, at multivariate analysis, it independently associated with HCC of metabolic origin ($p<0.05$), suggesting *D-loop* as a MASLD-specific biomarker. Conversely, ccf-COXIII levels significantly increased in all HCC patients with cirrhosis, independently of etiology ($p<0.0001$), supporting that its release is primarily driven by advanced tissue damage. The *D-loop* based prediction model, generated with RF, for HCC risk and applied to the entire cohort reached a higher AUC (78%) compared to reference scores, but without reaching the statistical significance, likely reflecting the biomarker's specificity for MASLD etiology. Conversely, the new diagnostic tool based on ccf-COXIII levels outperformed existing non-invasive tests, for HCC detection across patients with mixed etiologies, demonstrating 85% of accuracy.

Conclusion:
High *D-loop* levels identify MASLD-HCC risk, even in noncirrhotic cases which are outside HCC clinical screening, while ccf-COXIII has a broader clinical utility for HCC monitoring in patients with different chronic liver diseases.

PO2-13-YI
Comparative performance of HCC risk scores in patients with cirrhosis in the Netherlands

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Background and aims:
Patients with cirrhosis are at high risk of developing HCC and are therefore recommended to undergo biannual HCC surveillance. Given the increasing prevalence of cirrhosis, individualized risk prediction would be helpful to identify patients in whom surveillance could be safely deferred. We assessed the performance of two HCC risk scores, the Toronto HCC risk Index (THRI) and aMAP score, in a multicentre study including patients with cirrhosis in the Netherlands.

Method:
We included adults with cirrhosis from three sites in the Netherlands. Exclusion criteria were follow-up <6 months, missing risk score data, or prior HCC. THRI and aMAP scores were calculated as previously reported, classifying patients into low, intermediate, and high-risk groups. Kaplan–Meier analysis was used to estimate cumulative HCC incidence according to risk score categories.

Results:
A total of 1,531 patients were included in this cohort. The most common liver disease etiologies were steatotic liver disease (SLD; n = 453, 29%), chronic hepatitis C (HCV; n = 283, 18%), chronic hepatitis B (HBV; n = 242, 16%), and immune-associated liver disease (IALD; n = 275, 18%). The majority were male (63%), and the median age was 53 years (IQR: 44–61). The median CTP score was 5 (IQR: 5–7), and 366 (24%) had a history of decompensation. A total of 195 (12.7%) developed HCC during a median follow-up of 5.4 years (IQR: 3.1–9.1). The cumulative incidence of HCC was 7.2% and 18.4% at 5 and 10 years. The median THRI was 200 (IQR: 136–254), and the number of patients classified as low, intermediate, and high-risk THRI was 269 (18%), 746 (49%), and 516 (34%). The 5-year cumulative incidence was 0.5%, 6.1%, and 12.2% for low, intermediate, and high THRI ($p < 0.01$). The median aMAP score was 55 (IQR: 49–61), and the number of patients classified as low, intermediate, and high-risk aMAP was 437 (29%), 645 (42%), and 449 (29%). The 5-year cumulative incidence was 2.9%, 6.0%, and 14.0% for low, intermediate, and high aMAP. Among the 437 with low aMAP, only 141 (32%) had a concomitantly low THRI. The 5-year cumulative incidence of HCC was higher in low-aMAP patients with intermediate or high THRI than in those with both low aMAP and low THRI (4.27% vs 0%, $p = 0.01$).

Conclusion:
THRI and aMAP can be used to stratify HCC risk in patients with cirrhosis, but THRI was the most effective at identifying patients with a negligible risk of HCC. Deferral of HCC surveillance should be considered in patients at low predicted risk based on THRI.

PO3-2-YI

Comparative diagnostic accuracy of hepatocellular carcinoma biomarkers: comprehensive meta-analysis with meta-regression.

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Background and aims:
Hepatocellular carcinoma (HCC) represents a leading cause of cancer-related mortality worldwide, with early detection crucial for improved outcomes. While numerous biomarkers have been developed for HCC detection, their comparative diagnostic performance and sources of heterogeneity across different populations and etiologies remain insufficiently characterized. We conducted a comprehensive meta-analysis with meta-regression to systematically evaluate diagnostic accuracy and identify factors influencing biomarker performance.

Method:
We performed meta-analysis using up-to-date meta-analyses covering different HCC biomarkers from studies spanning 2003-2023. We employed random-effects models to calculate pooled area under the receiver operating characteristic curve (AUROC) estimates and conducted meta-regression analysis to explore relationships between diagnostic accuracy and study characteristics, including publication year, geographic location, study methodology, and patient characteristics.

Results:
Analysis yielded 183 biomarker-specific analyses from 105 unique studies evaluating twelve distinct biomarker approaches, encompassing 34,991 participants with 11,177 HCC cases. Among established biomarkers, glypican-3 (GPC3) plus alpha-fetoprotein (AFP) demonstrated highest pooled AUROC of 0.928 (95% CI: 0.915-0.941) across 25 studies, followed by dickkopf-1 (DKK-1) plus AFP at 0.920 (95% CI: 0.890-0.950) across 10 studies. Etiology subgroup analysis confirmed galectin-3 binding protein, AFP, lectin-reactive fraction of AFP, age and gender (GALAD) and DKK-1 plus AFP as strongest predictors in metabolic dysfunction-associated steatotic liver disease (MASLD) population (AUROC 0.940). Meta-regression revealed significant associations between diagnostic performance and geographic location ($p = 0.008$), with Western populations showing superior performance. Study methodology significantly influenced results ($p = 0.009$), while publication year showed no temporal trend ($p = 0.456$).

Conclusion:
This comprehensive meta-analysis provides definitive evidence supporting combination biomarker approaches over individual markers. Geographic and methodological factors significantly influence diagnostic performance, confirming need for population-specific validations and standardized protocols for optimal clinical implementation.

PO3-3
Remaining chronic hepatitis C treatment gaps impact on the care cascade of HCV related hepatocellular carcinoma

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Background and aims:
Direct-acting antivirals (DAAs) for hepatitis C (HCV) became universally available in Australia in 2016, but the impact of HCV cure on the presentation and outcomes of HCV-related hepatocellular carcinoma (HCV-HCC) remains unclear. This study examined the HCV care cascade among people with HCV-HCC and assessed the impact of sustained virological response (SVR) on tumour stage, treatment, and survival.

Method:
Incident HCC cases from six Melbourne tertiary hospital networks (2018–2021) were retrospectively identified and followed to October 2023. HCC was diagnosed by histopathology or LIRADS imaging with multidisciplinary team (MDT) consensus. SVR was confirmed by negative HCV RNA or documentation. Statistical analyses included Chi-square, Wilcoxon rank-sum, and Cox regression.

Results:
Of 1,013 HCC cases, 35% (n=348) were HCV-related. HCV-HCC cases were younger (median 61 vs 70 years, p<0.0001) and more likely to have cirrhosis (95% vs 77%, p<0.0001) and prior surveillance (45% vs 37%, p=0.012). Among HCV-HCC cases, 61% achieved SVR, with a median 2.9 years from SVR to HCC diagnosis. Those with SVR had less prior alcohol misuse (27% vs 43%, p=0.003) and injecting drug use (26% vs 41%, p=0.003), and were more likely to undergo surveillance (64% vs 18%, p<0.001), present with early BCLC stage (59% vs 40%, p=0.001), and receive curative therapy (40% vs 27%, p=0.015). Mortality was lower in the SVR group (42% vs 59%, p=0.004) with longer median survival (11.9 vs 6.0 months, p=0.02). SVR was associated with improved overall survival (HR 0.57, 95% CI 0.41–0.79, p=0.001), but this was not significant after adjustment for age, liver function, and tumour stage (aHR 0.79, 95% CI 0.54–1.15, p=0.22).

Conclusion:
Despite DAA availability, many people with HCV-HCC remain untreated, undiagnosed with cirrhosis, or unscreened for HCC. Achieving SVR is linked to earlier-stage HCC and better survival, underscoring the need for improved HCV detection, fibrosis assessment, and surveillance to reduce HCV-HCC mortality.

PO3-4-YI
HCC incidence and risk stratification in patients with metabolic dysfunction-associated steatotic liver disease on long-term follow-up: a retrospective multicentre study

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Background and aims:
Metabolic dysfunction-associated steatotic liver disease (MASLD) is projected to become the leading cause of hepatocellular carcinoma (HCC) globally. We aimed (i) to investigate the incidence of HCC in patients with MASLD according to baseline liver disease severity, and (ii) to assess the performance of non-invasive and biomarker-based prognostic tools for HCC prediction and risk stratification.

Method:
We retrospectively enrolled 942 consecutive patients with MASLD (median age: 60 [IQR 51–67] years; males: 553 [58.7%]; T2DM: 516 [54.8%]; median BMI: 30.8 [27.7–34.1] kg/m^2) and significant liver fibrosis (liver stiffness measurement [LSM]≥8 kPa or F≥2 at liver biopsy). Of these, 680 (72.2%) met criteria for compensated advanced chronic liver disease (cACLD; LSM ≥10 kPa or F≥3 at liver biopsy), within which 344 (50.6%; 36.5% of the overall cohort) had cirrhosis by clinical or histologic criteria. All patients had at least 6 months of follow-up (FU) with regular ultrasound surveillance. At baseline, we computed the Fibrosis-4 (FIB-4) score, the aMAP prognostic index, and the age-sex-AFP-PIVKA-II (ASAP) score. Serum AFP and PIVKA-II were centrally measured by CLEIA (Lumipulse®G600II, Fujirebio) under blinded conditions.

Results:
During a median FU of 2.4 (IQR 1.0–4.3) years, 49/942 (5.2%) patients developed HCC (incidence rate [IR]: 1.67 per 100 person/years [PY]). At baseline, 36/49 (73.5%) had cirrhosis, 12/49 (24.5%) had F3 fibrosis, and 1/49 (2.0%) had F2 fibrosis. The HCC IR among patients with liver cirrhosis was 3.75 per 100 PY, while among patients with F3 and F2 fibrosis was 1.09 and 0.11 per 100 PY, respectively. At HCC diagnosis, BCLC stage was 0 in 11 (22.4%) patients, A in 25 (51.0%), B in 5 (10.2%), C in 2 (4.1%);

BCLC stage was unknown in 6 patients. In the overall population, the integrated area under the curve (iAUC) from 1 to 5 years was 0.794 (95% CI 0.694–0.884) for aMAP, 0.792 (95% CI, 0.710–0.859) for ASAP, and 0.730 (95% CI 0.625–0.833) for FIB-4. Among patients with cACLD, the corresponding iAUC values were 0.759 (95% CI 0.643–0.865), 0.758 (95% CI 0.664–0.837), and 0.698 (95% CI 0.564–0.816), respectively. aMAP and ASAP score outperformed FIB-4 in both the overall cohort and the cACLD subgroup.

Conclusion:
Our results support HCC surveillance in MASLD patients with advanced liver disease; aMAP and ASAP score may help to define personalized, risk-adapted surveillance according to individual HCC risk.

PO3-5-YI
ESC and CARDIOSOR scores as easy tools to stratify cardiovascular risk in patients with HCC treated with atezolizumab/bevacizumab

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Background and aims:
The management of comorbidities has gained relevance in hepatocellular carcinoma (HCC) due to improved long-term survival. Bevacizumab, an anti-VEGF drug, increases the risk of major adverse cardiac events (MACE). Identifying at-risk patients is crucial since anti-VEGF-free therapeutic alternatives are now available. This study aimed to assess whether the European Society of Cardiology

(ESC) antiangiogenic risk score and the CARDIOSOR score (Carballo-Folgoso, 2021) predict MACE in patients with HCC treated with atezolizumab/bevacizumab (AB).

Method:
We retrospectively analyzed prospectively collected data from the multicentric Italian ARTE dataset, including patients treated with AB for unresectable HCC between June 2022 and July 2025. MACE occurrence was evaluated using a competing risk regression, considering non-cardiovascular death as a competing event.

Results:
Among 538 patients (median age 69.8 years), the prevalence of arterial hypertension and obesity was 56.3% and 18.4%, respectively. Moreover 7.6% had chronic coronary artery disease. Median follow-up was 22.4 months (95% CI 21.0-24.2 months) and median overall survival 19.7 months (95% CI 17.1-22.3). Twenty MACE (3.7%) occurred: 8 cerebrovascular accidents, 7 acute coronary syndromes, 3 strokes, and 2 heart failures. The cumulative incidence of MACE was 10.6%, 3.7%, 2.6%, and 0.7% in very high, high, medium and low risk groups according to the ESC score (sHR 3.80, 95% CI 1.52–9.45, p=0.004). Patients with a high-risk CARDIOSOR score also had an increased risk of MACE (sHR 2.70, 95% CI 1.08–6.74, p=0.03). The two scores performed similarly when we analyzed the goodness of fit achieving an Akaike and Bayesian information criteria of 235 and 239 and 241 and 245.

Conclusion:
These findings suggest that the ESC and CARDIOSOR scores could be used to stratify the risk of MACE in patients receiving AB. These tools might inform clinicians and provide relevant information when evaluating the choice of the first line regimen.

PO3-12-YI
Bridging the gap between locoregional and systemic therapy: a systematic review on transarterial chemoembolization with immune checkpoint inhibitors in intermediate-stage hepatocellular carcinoma

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Background and aims:
Transarterial chemoembolization (TACE) is the standard treatment for intermediate-stage (BCLC-B) hepatocellular carcinoma (HCC). Yet, it is associated with high recurrence rates as post-TACE hypoxia fosters an immunosuppressive tumor microenvironment mediated by VEGF and PD-L1. The addition of immune checkpoint inhibitors (ICI) has emerged as a promising strategy. In light of recently published evidence, this systematic review (SR) aims to evaluate the efficacy and safety of TACE combined with ICI in BCLC-B HCC versus TACE alone.

Method:
This SR followed PRISMA guidelines. Databases searched were PubMed, Embase and Cochrane, for articles published up to October 2025, including adults with BCLC-B HCC treated with TACE plus ICI. Outcomes were ORR (Objective Response Rate), DCR (Disease Control Rate), PFS (Progression Free Survival) and OS (Overall Survival). Risk of bias was evaluated. Results were summarized qualitatively. PROSPERO ID: CRD420251169381.

Results:
This SR included eight studies (2 RCTs, 2 phase II, 4 retrospective cohorts), with 1997 patients. In phase III trials, the combination prolonged PFS versus control, one study reporting 14.6 vs 10.0 months (HR 0.66, 95%CI 0.51 – 0.84; p = 0.0002) and another 14.5 vs 8.5 months (HR 0.64, 0.50 – 0.83). ORR also favored the intervention by RECIST 1.1 (BICR) 46.8% (intervention) vs 33.3% (control) (Δ 13.5%, p = 0.0005) and by mRECIST 71.3% vs 49.8% (Δ 21.5%, p = 0.0001). OS showed a positive trend but not statistically significant in one study (HR 0.80; p = 0.087). Across non-randomized studies, median PFS ranged 9 – 18 months, with higher disease control (phase II DCR 95%; cohorts ORR 55 – 67%) and consistent advantages versus TACE cohorts (e.g., 15.0 vs 8.2 months). Safety was manageable; the most frequent adverse events were transaminase elevation, hypertension and thrombocytopenia. Collectively, results across designs indicate greater response and PFS with TACE plus ICI and acceptable as well as similar toxicity, compared to TACE alone.

Conclusion:
The combination of TACE and ICI has shown improvement in analyzed outcomes among BCLC-B patients, while maintaining manageable safety profiles. The evidence reinforces that this association could bridge locoregional and systemic treatments capable of redefining the management of BCLC-B HCC. However, rigorous trials targeting BCLC-B patients are required to compare sequential to concomitant strategies, which are essential to consolidate its role and guide evidence-based clinical decisions.

PO3-13
The impact of extrahepatic metastases in patients with hepatocellular carcinoma: A longitudinal analysis

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Background and aims:
Extrahepatic metastatic disease (EMD) in patients with hepatocellular carcinoma (HCC) is classified as advanced stage by BCLC. Evidence on prognostic impact of EMD is limited. We investigated the prognostic relevance of EMD — with a special focus on anatomical sites — using a longitudinal approach.

Method:
Patients with HCC treated between 01/2007-12/2021 were included. All cross-sectional imaging was re-evaluated by a radiologist to determine the timing and anatomical sites of EMD. Overall survival (OS) was analysed using a multivariable Cox model with site-specific metastases as time-dependent covariates, adjusting for established risk factors.

Results:
Of 1,563 patients included, 429 (27.4%) had EMD: 190 (12.2%) at diagnosis (synchronous) and 239 (15.3%) during follow-up (metachronous). Median OS was 5.6 months with synchronous EMD vs 20.0 months in those without EMD or with metachronous EMD ($p<0.001$). The distribution of metastatic sites and corresponding hazard ratios (HR, 95% CI) was: lung (n = 183; HR = 1.62 (CI = 1.32-2.00)), regional lymph nodes (n = 168; HR = 1.55 (CI = 1.27-1.90)), bone (n = 102; HR = 1.37 (CI = 0.84-2.25)), peritoneum (n = 101; HR = 1.78 (CI = 1.40-2.27)), adrenal glands (n = 79; HR = 1.42 (CI = 1.02-1.99)), distant lymph nodes (n = 53; HR = 2.38 (CI = 1.74-3.27)), and soft tissue (n = 43; HR = 1.79 (CI = 1.23-2.60)). Metastases at the sites lung, lymph nodes, peritoneum, adrenal glands, and soft tissue were independent predictors of survival. Each additional site increased the HR by 1.64 (95% CI: 1.54-1.74).

Conclusion:
Importantly, the presence of any metastasis is associated with adverse outcomes and an unfavorable hazard ratio. However, bone involvement appears comparatively less detrimental than other forms of extrahepatic spread, whereas distant lymph node metastases are particularly unfavorable. Moreover, prognosis deteriorates progressively with the number of metastatic sites, with each additional site conferring a substantial increase in risk. Thus, regular re-staging with detailed imaging evaluation is crucial.

PO3-14-YI
Distinct cardiometabolic profiles drive divergent hepatocellular carcinoma risk trajectories in advanced fibrosis-affected metabolic dysfunction–associated steatotic liver disease (MASLD) patients

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Background and aims:
Metabolic dysfunction (MD)-associated steatotic liver disease (MASLD) is defined by steatotic liver disease (SLD) in the presence of at least one cardiometabolic risk factor (CMRF)—obesity, type 2 diabetes, dyslipidemia, or hypertension—in the absence of alternative causes. MASLD may progress to steatohepatitis (MASH) and advanced fibrosis (AF), significantly increasing the risk of hepatocellular carcinoma (HCC). While cardiovascular risk is known to escalate with MD severity, the impact of cumulative CMRF burden on HCC development remains poorly characterized. This study aimed to assess differential HCC risk and timing by stratifying MASLD-AF patients according to distinct CMRF combinations.

Method:
Biochemical, clinical, and Liver Stiffness (LSM) data from 1921 SLD individuals, archived in the Health Documents Digitization Repository of the “Luigi Vanvitelli” University Hospital (January 2010 – Oct 2020), were retrospectively analyzed to identify subjects fulfilling EASL-proposed MASLD criteria and exhibiting LSM-AF. A non-redundant permutation of CMRFs—obesity (Obe), dysglycaemia or type 2 diabetes (Gly), dyslipidemia (Lip), and elevated blood pressure (Press)—was applied, yielding 4 groups with 15 distinct MD profiles: Group 1) One CMRF (n: 311) [1a: Obe (n: 130); 1b: Gly (n: 40); 1c: Lip (n: 91); 1d: Press (n: 50)]; Group 2) Two CMRFs (n: 840) [2a: Obe-Gly (n: 140); 2b: Obe-Lip (n: 120); 2c: Obe-Press (n: 150); 2d: Gly-Lip (n: 130); 2e: Gly-Press (n: 140); 2f: Lip-Press (n: 160)]; Group 3) Three CMRFs (n: 680) [3a: Obe-Gly-Lip (n: 190); 3b: Obe-Lip-Press (n: 170); 3c: Obe-Gly-Press (n: 140); 3d: Gly-Lip-Press (n: 180)]; Group 4) Four CMRFs (Obe-Gly-Lip-Press) (n: 90). HCC diagnosis and staging (BCLC) were retrospectively recorded over a 5-year follow-up.

Results:
Patients with ≥3 CMRFs exhibited significantly higher HCC risk [HR: 3.12, p: 0.001]. Within this subgroup, Gly-Lip-Press, Obe-Gly-Lip [HR: 1.129, p: 0.034], and Obe-Gly-Lip-Press [HR: 2.21, p: 0.002] showed progressively increasing 5-year HCC incidence and decreasing median time to occurrence (48.2 vs 41.3 vs 28.1 months; $p < 0.0001$). Notably, the BCLC-C stage at diagnosis was more frequent in Obe-Gly-Lip (31%) compared to other Group 3 profiles (< 10%; $p < 0.0001$).

Conclusion:
CMRF-based stratification reveals substantial heterogeneity in HCC risk among MASLD-AF patients, supporting the implementation of personalized surveillance strategies taking into account the metabolic burden.

PO3-15-YI
Post-Cholecystectomy Syndrome affects Ultrasound Visualization in Non-Obese Viral-Related advanced chronic liver disease: implications of gallbladder removal for Li-RADS-based HCC surveillance

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Background and aims:
The LI-RADS Visualization Score (Li-RADSVS) standardizes ultrasound (US) adequacy for hepatocellular carcinoma (HCC) surveillance in advanced chronic liver disease (ACLD), distinguishing score A (optimal), B (suboptimal), and C (poor visualization). Scores B/C reduce US sensitivity, prompting Magnetic Resonance Imaging (MRI)/ Computerized Tomography (CT) use. Severe obesity and Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD)-related steatosis are known to impair Li-RADSVS.

Post-cholecystectomy syndrome (PCS), characterized by continuous bile flow, altered motility, and meteorism, may hinder hepatic US visualization. However, its impact on Li-RADSVS in non-obese, non-MASLD viral-related ACLD remains unexplored.

Method:
Hospitalized non-obese, non-MASLD viral-related (chronic HBV/HCV infection) cACLD patients were enrolled into observation (Obs, 2015 – 2020, n: 106) and validation (Vld, 2021 – 2025, n: 102) cohorts. ACLD diagnosis was confirmed by liver stiffness measurement (LSM > 15 kPa). Demographic, clinical, pharmacological, and surgical data were collected; patients on UDCA or antimeteorics were excluded. After a 3-day standardized diet, fasting US was performed on day 4 by three blinded operators assigning Li-RADSVS (A/B/C) via electronic case report forms. Interobserver agreement (Cohen's kappa) was assessed. Patients were stratified by cholecystectomy status (PCS vs no-PCS). Obs patients with a unanimous score C underwent MRI/CT, and the focal liver lesion (FLL) missing rate (i.e., FLL undetected by none of the three operators) was evaluated.

Results:
Weighted Cohen's kappa ranged from 0.40 – 0.70 (Obs) and 0.38 – 0.72 (Vld). PCS prevalence was 40.2% (Obs) and 38.2% (Vld), with significantly higher score C rates vs no-PCS (Obs: 44% vs 23%, p = 0.034; Vld: 42% vs 21%, p: 0.027). Multivariate analysis (adjusted for sex, age, Body Mass Index, etiology) identified prior cholecystectomy as independently associated with poor visualization [Obs: aHR 1.325, p: 0.002; Vld: aHR 1.221, p: 0.001], along with time since surgery > 2 years [Obs: aHR 1.105, p: 0.031; Vld: aHR 1.136, p: 0.038]. In Obs score C patients undergoing CT/MRI, FLL missing was reported in 39% of cases.

Conclusion:
Prior cholecystectomy significantly impairs US visualization in non-obese, non-MASLD viral-related ACLD, reducing Li-RADSVS and impacting HCC surveillance accuracy.

PO3-16
Impact of expanded liver transplant criteria in the Brazilian population – Is there a better option than Milan Brazil criteria?

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Background and aims:
Liver transplantation (LT) is considered the treatment with the highest curative potential for hepatocellular carcinoma (HCC), with the Milan Criteria (MC) being the most widely used for patient selection. Due to the restrictive nature of MC, several expanded criteria have been proposed to identify patients beyond MC who may still benefit from LT. In Brazil, the Milan Brazil Criteria (MBC) are adopted as an expanded model, but they are associated with a higher risk of post-LT recurrence compared to MC. Our aim was to compare the performance of the expanded criteria Metroticket 2.0, AFP model, Up-to-7 and MBC in predicting post-LT HCC recurrence and overall survival, compared to the traditional MC.

Method:
This was a retrospective multicenter cohort study including 1,059 patients who underwent LT for HCC in Brazil. Patients were classified according to MC and expanded criteria both at diagnosis and at explant, and were evaluated for recurrence-free survival (RFS) and overall survival (OS). Patients with AFP >1,000 ng/mL or missing data were excluded.

Results:
At diagnosis (n = 574), 88% of patients were within MC, 6% were beyond MC but within MBC, and 6% were beyond both criteria. Patients within MC had 5-year RFS of 92% and OS of 76.8%. Among those beyond MC, MBC patients showed a threefold higher risk of recurrence (68.5%; HR = 3.07, 95% CI 1.29–7.34, p = 0.011) and worse 5-year OS (41.1%; p = 0.003). In contrast, patients within Up-to-7 had no significant increase in recurrence risk (p = 0.113) or difference in OS (p = 0.753) compared with MC. The Metroticket 2.0 model also showed no difference in RFS (84.7%; p = 0.873) or OS (74.8%; p = 0.688). Similarly, the Up-to-7 + AFP ≤ 400 ng/mL criteria presented RFS of 77.8% (p = 0.113) and OS of 66.7% (p = 0.753). The AFP model demonstrated no OS difference (p = 0.64) but doubled the recurrence risk (HR = 2.52, 95% CI 1.16–5.45, p = 0.019). When assessed at explant (n = 745), both Metroticket 2.0 and Up-to-7 + AFP ≤ 400 ng/mL showed comparable OS to MC.

Conclusion:
The expanded criteria Up-to-7 + AFP ≤ 400 ng/mL and Metroticket 2.0 outperformed MBC in identifying suitable LT candidates beyond MC. Larger cohorts are needed to confirm these findings.

PO3-17-YI
Interim clinical outcomes from a prospective cohort study of stereotactic body radiotherapy for hepatocellular carcinoma at a university hospital in Chile

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Background and aims:
Stereotactic body radiotherapy (SBRT) represents an effective locoregional treatment in patients with hepatocellular carcinoma (HCC) who are not eligible for other treatments, as established in multiple clinical guidelines in recent years. To date, prospective data from Latin America are scarce. We report a preplanned interim analysis from a prospective, single-institution phase II study designed to validate clinical outcomes of SBRT for HCC and to enable future biomarker discovery.

Method:
An interim analysis of an ongoing prospective, IRB-approved, single-institution, phase II study aiming at validating previously published outcomes of SBRT for HCC in previous prospective studies. Patients were eligible if they had radiologically confirmed HCC, liver function A5 to C10 as per the Child Pugh score, and were ineligible to receive other locoregional therapies due to disease extent, previous treatment failure, medical comorbidities, or difficulty in access. Biospecimen collection for biomarker analysis is ongoing and not included in this interim report. Data cutoff was October 16, 2025.

Results:
From September 2023 to June 2025, 53 patients have been accrued, of whom 2 withdrew consent after starting treatment and had SBRT off-protocol, and 2 patients were lost to follow-up. The median age was 67 years (range: 56,9 to 90,9 years). All patients had liver cirrhosis, and the cause of liver disease was metabolic dysfunction-associated steatotic liver disease (MASLD) in 39 patients, MetALD in 3 patients, alcohol-related in 2 patients, and others in 6 patients. 35 patients had CPA5 liver function, 8 had B6, and 6 had B7 or worse. 28 patients had Barcelona Clinic Liver Cancer (BCLC) stage A HCC, 52% had a single HCC, and the median HCC size was 4.4 cm. (48.7 cc). Median SBRT dose was 45Gy (range: 27.5 to 50Gy), and the median number of fractions was 5 fractions (range: 5 to 15 fractions). Overall survival (OS) at 1 year was 87%, local control (LC) at 1 year was 93%, and disease-free survival at 1 year was 60%. No patients have developed GI bleeding related to SBRT. In the absence of disease progression, only 1 patient had worsening of liver function of two or more points in the first three months after SBRT.

Conclusion:
To our knowledge, this is the first prospective SBRT study for HCC reported from Latin America. In a selected population, SBRT achieved 1-year OS and LC comparable to published series, with low early hepatic and gastrointestinal toxicity.

PO4-1-YI

When patients with cirrhosis and hepatocellular carcinoma meet the emergency room: clinical phenotypes and 28-day outcomes across acute-event clusters

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Background and aims:
Emergency presentation in hepatocellular carcinoma (HCC) often reflects acute decompensation or intercurrent conditions that determine short-term prognosis. The heterogeneity and prognostic impact of these acute events are poorly defined. This study characterized 28-day outcomes and clinical phenotypes of HCC patients presenting to the emergency department (ED).

Method:
We retrospectively analyzed 1,076 consecutive HCC patients admitted to the ED between 2017 and 2025 at IRCCS Fondazione Policlinico A. Gemelli (Rome, Italy). Patients were classified into five clusters according to the main reason for presentation: major adverse liver event (MALE, n = 426), major adverse cardiovascular event (MACE, n = 99), sepsis (n = 306), urgent surgery (n = 72), and non-septic infections or other causes (n = 171). Survival up to 28 days was estimated by Kaplan–Meier analysis with pairwise log-rank tests. Clinical characteristics were compared after variable normalization, and predictive accuracy of CLIF-AD and MELD-Na scores for 28-day mortality was assessed by ROC analysis.

Results:
Within 28 days, 92 deaths (8.6%) occurred. Mortality differed significantly across clusters ($p < 0.001$). The MALE group showed the poorest survival (48 deaths, 11.3%), significantly lower than non-septic infections ($p = 0.0023$) and surgery ($p = 0.0093$). Sepsis was also associated with high early mortality (27 deaths, 8.8%; $p = 0.0267$ vs infections/others). MACE (9 deaths, 9.1%) and urgent surgery (6 deaths, 8.3%) had more favorable outcomes without significant differences versus reference. Distinct clinical patterns emerged: MALE patients had the highest MELD-Na and bilirubin, frequent portal hypertension, anemia and thrombocytopenia, indicating advanced liver failure. Sepsis showed pronounced inflammation with elevated leukocytes and moderate liver dysfunction. MACE patients were older with more comorbidities, while surgical cases showed better hepatic function. Non-septic infections displayed the mildest phenotype. CLIF-AD and MELD-Na scores showed similar moderate performance in predicting 28-day mortality.

Conclusion:
Among over one thousand HCC patients presenting acutely to the ED, the precipitating event defined distinct clinical phenotypes with markedly different 28-day outcomes. Major liver events and sepsis were associated with the highest early mortality, whereas cardiovascular and surgical presentations occurred in patients with better hepatic reserve.

PO4-3
Complementary evaluation of phase III Immunotherapy trials in advanced HCC using the Survival-Inferred Fragility Index

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Background and aims:
Hepatocellular carcinoma (HCC) represents a major global health burden, historically treated with tyrosine kinase inhibitors. Recent advances in immune checkpoint inhibitors (ICIs) have transformed management, with pivotal trials such as IMbrave150 and HIMALAYA establishing ICI-based combinations as first-line therapy. However, traditional statistical metrics may not fully capture the robustness of trial results. The Survival-Inferred Fragility Index (SIFI) provides a measure of trial stability by calculating the minimum number of additional survival events needed in the experimental arm to nullify statistical significance.

Method:
We systematically searched PubMed, Embase, and Scopus for phase III randomized controlled trials comparing ICIs and TKIs in HCC published until 31 May 2025. Studies with statistically significant time-to-event outcomes were included. Individual survival data were reconstructed from Kaplan–Meier curves using validated methods, and SIFI was calculated using specific R algorithms.

Results:
Seven studies including 5,238 patients were analyzed. For overall survival, the median SIFI was 9.1 (range 3–14.5), with four of seven trials showing SIFI <10, including two with SIFI <2 (LEAP-002, CheckMate 9DW). For progression-free survival, the median SIFI was 8.8 (range 5–10.8), with three of four evaluable studies <10. In five trials, SIFI represented <1% of enrolled patients, with the lowest relative values in LEAP-002 (0.1% for OS; 0.2% for PFS), CheckMate 9DW (0.3%), and HIMALAYA (0.4%). ORIENT-32 and CARES-310 showed greater robustness (SIFI 20 and 16).

Conclusion:
SIFI analysis demonstrates heterogeneous stability across pivotal HCC trials. Incorporating fragility indices alongside traditional metrics may enhance transparency and support balanced interpretation of trial outcomes.

PO4-4-YI

Glucagon-like peptide-1 receptor agonists for hepatocellular carcinoma prevention in type 2 diabetes: systematic review and meta-analysis.

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Background and aims:
While glucagon-like peptide-1 receptor agonists (GLP-1RAs) show promise for hepatoprotection in type 2 diabetes mellitus (T2DM), the magnitude of hepatocellular carcinoma (HCC) risk reduction and optimal patient selection remain unclear. We conducted comprehensive meta-analysis to quantify GLP-1RA efficacy in HCC prevention and inform clinical implementation strategies.

Method:
We systematically searched PubMed, Embase, and Web of Science through June 2025 for cohort studies comparing HCC incidence between GLP-1RA users and non-users with T2DM. Random-effects meta-analysis, network meta-analysis, and meta-regression were performed. Heterogeneity was explored through stratified analyses and quantitative bias assessment.

Results:
Nine studies encompassing 2,283,835 total patients (analyzed cohorts: 1,012,482) were included. GLP-1RA use was associated with 42% reduced HCC risk (pooled hazard ratio [HR] 0.60, 95% CI: 0.41-0.88; I-squared =86.2%). Effect magnitude varied significantly by comparator: versus insulin (HR 0.29, 95% CI: 0.13-0.67), versus oral agents (HR 0.81, 95% CI: 0.63-1.05), versus no treatment (HR 0.77, 95% CI: 0.52-1.14). Meta-regression identified insulin as comparator as primary driver of heterogeneity, explaining 55% of between-study variance. Benefits were greatest in patients without cirrhosis (HR 0.41, 95% CI: 0.29-0.58). Network meta-analysis ranked GLP-1RAs highest for HCC prevention (surface under the cumulative ranking curve [SUCRA] 0.89), with insulin ranking lowest (0.08). Number needed to treat ranged from 24-476.

Conclusion:
GLP-1RAs substantially reduce HCC risk in T2DM, with benefits partly attributable to avoiding insulin's potential hepatotoxicity. These findings support preferential use of GLP-1RAs over insulin in patients at HCC risk.

PO4-7-YI
GAAD score as a diagnostic and prognostic marker from cirrhosis to hepatocellular carcinoma

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Background and aims:
Early recognition of patients at increased risk of hepatocellular carcinoma (HCC) within chronic liver disease remains a major unmet clinical challenge. The GAAD score, based on gender, age, AFP and PIVKA-II, is a diagnostic algorithm designed to enable earlier detection of HCC and improve survival, generating a 0–10 score indicative of HCC risk (positive if >2.57). This study assessed the diagnostic and prognostic performance of GAAD across the clinical spectrum of liver cirrhosis (LC) and HCC.

Method:
A retrospective analysis was conducted on 234 subjects: non-evolutive LC (NELC=107), evolutive LC (patients who developed HCC, ELC=32), and HCC (n=95). AFP and PIVKA-II were measured and GAAD scores were calculated. GAAD scores and clinical parameters were compared across groups and within HCC subcategories (lesion type, BCLC stage, etiology). Diagnostic accuracy was evaluated by ROC analysis, including solitary nodules <2 cm, and correlations evaluated with Spearman's rho.GAAD-based stratification was used to model competing risks for death or liver transplantation in HCC patients and to assess HCC-free survival analysis in those without HCC at baseline.

Results:
ROC analysis showed excellent diagnostic performance for HCC (AUC = 0.88, sensitivity 83%, specificity 82.9%) and a good accuracy for solitary nodules <2 cm (AUC = 0.76), outperforming standard biomarkers, including GALAD score. GAAD progressively increased along disease stages: median [IQR] 1.81 [0.35–2.94] in non-evolutive LC, 1.96 [0.62–2.84] in evolutive LC, and 6.69 [3.44–9.17] in HCC ($p < 0.0001$). Within HCC, GAAD correlated with tumor burden ($p = 0.04$) and BCLC stage ($p = 0.01$), but not with etiology ($p = 0.58$). Serum GAAD and PIVKA-II levels showed a significant positive correlation with the maximum tumor diameter ($r = 0.457$ and $r = 0.503$, respectively; $p < 0.001$). Higher GAAD scores at the diagnosis of HCC were associated with lower overall survival ($p = 0.007$). Patients with LC and higher GAAD values are at major risk to develop HCC within 24 months (p=0.044), and GAAD positive patients with LC had lower HCC-free survival time compared to those with GAAD negative values (p=0.003).

Conclusion:
GAAD provides reliable diagnostic and prognostic information across cirrhosis and HCC, supporting its integration into dynamic surveillance strategies for personalised risk assessment. Further evaluation of its performance in early-stage HCC in larger populations is warranted.

PO4-8-YI
Assessing early HCC recurrence after liver transplantation: The predictive value of 18F-FDG PET/CT and microvascular invasion

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Background and aims:
Liver transplantation (LT) is the most effective treatment against hepatocellular carcinoma, but recurrence remains challenging. Traditional criteria based on tumor size, nodule number and AFP levels have limited success in predicting aggressiveness. 18F-FDG PET/CT has shown promise in identifying high-risk tumor features, including microvascular invasion (MVI), a key predictor of recurrence.

Method:
In this retrospective, single-center study, all consecutive patients who underwent LT for HCC between 2010 and 2019 were included. During pre-LT work-up all patients underwent 18F-FDG PET/CT and, following the LT, explant pathology was analyzed for MVI and other histological features. The primary endpoint was to identify predictors of early HCC recurrence (within 24 months after LT). Secondary endpoints included identifying predictors of high-risk histological features at explant, describing recurrence patterns, and assessing post-recurrence survival.

Results:
The study included 143 patients (median age 59 years [IQR 54-64], 85% males, , median MELD 10 [IQR 8-14], median AFP value 8.5 [IQR 4-39] ng/ml. Forty (28%) HCC resulted 18F-FDG PET/CT positive and 25 (17%) developed HCC recurrence post-LT (median post-LT follow-up 49 months [IQR 28.5-77]), with 12 (48%) experiencing early recurrence. MVI at explant was independently associated with early recurrence (HR: 7.20, 95% CI 1.82-28.45, p=0.005), while intra-hepatic 18F-FDG PET/CT positivity within six months before LT independently predicted MVI at explant (OR 3.90, 95% CI 1.30–11.71, p=0.01).

Conclusion:
18F-FDG PET/CT is a valuable tool for pretransplant risk assessment, predicting MVI, and indirectly predicting early recurrence. Its incorporation into the selection criteria for LT may enhance patient stratification and post-transplant outcomes.

PO4-9
p62/SQSTM1 expression is an independent marker of poor prognosis in a European hepatocellular carcinoma cohort

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Background and aims:
p62/SQSTM1 is a multifunctional protein involved in autophagy, proteasomal degradation and tumorigenesis. p62 is also a major constituent of hepatocellular inclusions - Mallory-Denk bodies (MDB), hyaline bodies (HB) - which may serve as markers of suppressed autophagy. Accumulation of p62 promotes activation of oncogenic pathways. There is scarce data regarding p62 expression in human hepatocellular carcinoma (HCC). We aimed to evaluate the prognostic significance of p62 expression in a well characterized Greek HCC cohort.

Method:
We retrospectively studied 97 HCC from 97 patients [77(79.4%) males, median age 72 (IQR 62-77, range 17-96) years] who underwent hepatectomy between 2001 and 2018 and were followed up for 52 months (range 2-161). Aetiology of underlying chronic liver disease was metabolic dysfunction 40.2%, hepatitis B virus 30.9%, hepatitis C virus 10.3%, alcohol-related 5.1% On histopathology review and re-staging (WHO 2019, AJCC 8th): grade 1 n=6(6.2%), 2 61(62.9%) & 3 30(30.9%), stage I 32%, II 39.2%, III 24.7% & IV 4.1%, background liver fibrosis stage F1 16.5%, F2 12.4%, F3 11.3%, F4 23.7%. The presence of MDB and HB was recorded. Immunostaining for p62 (clone D3, Santa Cruz Biotechnology, Dallas, TX, USA) was applied on tissue microarrays with a threshold for p62 positivity >5% tumour cells. The prognostic impact of p62 immunoxpression was assessed using Kaplan-Meier and multivariate Cox proportional models. For statistical correlations $p<0.05$ was considered significant.

Results:
MDBs, HB or both were present in 10(10.3%), 33(34%) or 8(8.2%) HCC, accordingly. p62 immunohistochemical expression was positive in 54(56.93%) HCC and was significantly higher in HCC compared to background liver ($p<0.001$). p62 overexpression was positively associated with HCC grade ($p<0.001$), pTNM stage ($p<0.001$) and microvascular invasion ($p=0.045$); there was no correlation with other clinico-pathological variables. Survival analysis showed significant association of p62 positivity with shorter overall survival ($p<0.003$). Stepwise Cox regression highlighted p62 expression as an independent prognostic marker in HCC ($p=0.011$,CI 1.283-6.739).

Conclusion:
p62/SQSTM1 expression emerged as an independent marker of poor prognosis in Greek HCC indicating that impaired autophagy may contribute to tumour aggressiveness in HCC. Further studies are underway to validate the prognostic significance of p62 overexpression in larger independent HCC cohorts.

PO4-10
IMreal Cohort 6: Interim analysis of patients with unresectable hepatocellular carcinoma (HCC) treated with first-line atezolizumab + bevacizumab in the real-world setting of routine clinical practice

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Background and aims:
The IMbrave150 trial established atezolizumab(atezo)+bevacizumab(bev) as a first-line (1L) standard of care (SOC) in patients (pts) with unresectable HCC. IMreal (NCT03782207) is a global, non-interventional, multi-cohort prospective study to assess effectiveness and safety of atezo+bev in the real-world setting (RWS) of routine clinical practice, bolstering existing real-world data. Here, we report an interim analysis (clinical cutoff 15 May 2024) of outcomes from IMreal Cohort 6 and ad hoc analyses in an IMbrave150-like population.

Method:
Enrolled pts had treatment-naive unresectable HCC treated with 1L atezo+bev with Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2, Barcelona Clinic Liver Cancer (BCLC) stage B-D and Child-Pugh (CP) score A-C. The primary endpoint was overall survival (OS) and 2-year (y) OS rate. Secondary endpoints included progression-free survival (PFS) and objective response rate (ORR). The IMbrave150-like population was defined as pts with ECOG PS 0/1, BCLC stage B/C and CP score A.

Results:
IMreal Cohort 6 enrolled 470 pts with unresectable HCC from 12 March 2021 to 21 June 2023 with a median time on study of 10.7 months (mo). The median age of enrolled pts was 67 y, and 45.9% (n = 140) had ECOG PS 0. In the IMbrave150-like population (n = 222), the median age was 69 y and 54.5% (n = 121) of pts had ECOG PS 0. In the FAS population (n = 461), median OS (mOS) was 14.5 mo (95% confidence interval [CI]: 12.7, 16.5), the 2-y OS rate was 32.6% (95% CI: 26.4, 38.8) and the median PFS (mPFS) was 7.3 mo (95% CI: 6.2, 8.1). The ORR was 28.8% (95% CI: 24.3, 33.6) in the response-evaluable population (REP, n = 382). The incidence of treatment-related adverse events (TRAE) was 51.0%; 78 pts (16.9%) had Grade 3/4 TRAEs. For the IMbrave150-like pts, mOS was 16.6 mo (95% CI: 13.6, 20.3) and the 2-y OS rate was 34.6% (95% CI: 25.0, 44.1). mPFS was 7.4 mo (95% CI: 6.2, 8.7). The ORR was 25.4% (95% CI: 19.4, 32.1) in the REP (n = 193). The incidences of TRAE and Grade 3/4 TRAE were 57.7% and 20.3%, respectively. No new safety signals observed.

Conclusion:
Although pts with unresectable HCC who received atezo+bev in this RWS included those who had prognostically unfavourable characteristics compared to the IMbrave150 trial, and the data being relatively immature, the effectiveness outcomes were generally similar reinforcing atezo+bev as a SOC treatment option in routine clinical practice. The safety profile was consistent with the known profiles of atezo and bev.

PO4-12
Peritumoral stiffness predicts early recurrence of hepatocellular carcinoma after transarterial chemoembolization

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Background and aims:
Estimation of peritumoral liver stiffness (LS) is emerging as a new means of predicting outcome of hepatocellular carcinoma (HCC) after curative or bridging procedures. The aim of this study is to determine whether peritumoral stiffness estimated by shear-wave elastography on abdominal ultrasonography can be used to predict HCC recurrence after transarterial chemoembolization (TACE).

Method:
We prospectively evaluated 87 patients diagnosed with hepatocellular carcinoma, evaluated in a single tertiary hepatology center. TACE was performed according to Barcelona Clinic Liver Cancer classification taking into account technical aspects and patient preference. 2D shear wave elastography was performed at day 1 and week 4 after the procedure. Peritumoral liver stiffness (LS) was calculated as means of liver stiffness determined at 6 different points surrounding the tumor, at a distance of 0.5-1cm. Recurrence was established by contrast enhanced CT or MRI performed at 3 and 6 months after TACE.

Results:
Mean age in the study group was 57.42 +/- 12.83 years, with a predominance of the male gender (58.6%). Underlying etiology of liver disease was: HBV infection (43.67%), HCV infection (36.78%), HBV and HDV infection (13.79%) and alcohol-related liver disease (5.74%). All patients were classified as liver cirrhosis (Child Pugh A 48 patients, Child Pugh B 37 patients). Day 1 peritumoral LS over 50.7 kPa was associated with increased risk of recurrence at 3 months (RR= 2.10, p=0.03) and at 6 months (RR= 2.42, p= 0.04). Week 4 Peritumoral LS over 42.1 was associated with increased risk of recurrence at 3 months (RR= 1.8, p= 0.02) and 6 months (RR= 2.3, p= 0.01). More importantly, a decrease in LS of over 10 KPa from day 1 to week 4 was negatively associated with recurrence (RR= 0.15, p<0.01).

Conclusion:
Estimation of peritumoral LS can predict early recurrence of HCC in patients undergoing TACE. This can be used to establish a personalized schedule of imagistic assessments and interventional procedures for HCC patients

PO4-13-YI
Multimodal deep learning for early prediction of disease progression in advanced hepatocellular carcinoma treated with atezolizumab-bevacizumab

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Background and aims:
Atezolizumab plus bevacizumab represents a standard first-line therapy for advanced HCC, but individual response remains heterogeneous and difficult to predict. We developed a multimodal artificial intelligence framework integrating clinical data and pre-treatment computed tomography imaging to predict six-month progression-free survival in patients receiving atezolizumab-bevacizumab.

Method:
We retrospectively analysed 62 patients with advanced HCC treated with first-line atezolizumab-bevacizumab at a tertiary referral centre (University of Palermo, Italy). A deep learning architecture combining a convolutional neural network for CT image analysis (arterial, venous, and delayed phases) with a multilayer perceptron for structured clinical variables was developed. The model was trained to predict progression-free survival status at six months. Performance was evaluated using accuracy, precision, recall, F1-score, balanced accuracy, and area under the receiver operating characteristic curve (AUROC). Results were compared with conventional logistic regression incorporating clinical variables alone.

Results:
After a median follow-up of 15.9 months, median overall survival was 24.3 months (95% CI: 15.9-38.0). Twenty-three patients (37.1%) experienced progression or death within six months. The multimodal model achieved an AUROC of 0.86, with 80.1% accuracy, 84.7% specificity, 68.9% sensitivity, 67.0% F1-score, and 76.8% balanced accuracy. In contrast, traditional logistic regression yielded an AUROC of 0.67 (95% CI: 0.54-0.78), with neoplastic portal vein invasion showing a trend toward significance (OR: 2.79, 95% CI: 0.98-7.92, p=0.053) in multivariable analysis.

Conclusion:
A multimodal artificial intelligence approach integrating CT imaging with clinical data demonstrates promising capability in predicting early disease progression in HCC patients treated with atezolizumab-bevacizumab. While preliminary and requiring external validation, these findings suggest that deep learning frameworks may enhance risk stratification and support personalized treatment decisions in advanced hepatocellular carcinoma.

PO4-15-YI

Patient perspectives and barriers in HCC surveillance: insights to guide implementation of patient-centred pathways

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Background and aims:
HCC is a rapidly growing cause of cancer mortality. Surveillance adherence is low with fewer than 25% receiving 6-monthly monitoring; reasons for this are not well understood. Our aim was to explore patient experiences to identify the specific mechanisms, barriers, and systemic gaps that contribute to low adherence; to guide the co-design and implementation of patient-centred pathways.

Method:
Exploratory qualitative methods included semi-structured interviews with patients in HCC surveillance at Manchester University NHS Foundation Trust. Purposive sampling ensured diversity across characteristics, and representation of patients with low adherence, high self-reported barriers, and no internet access. Thematic analysis was performed in NVivo. This study was part of REVISE HCC (NCPC02013) – a prospective study implementing the GAAD algorithm in real world surveillance.

Results:
Participants (n=20) were age (median 65); male (55%); white (80%), asian (15%); from urban (95%) and deprived areas (median IMD decile 3.5); MASLD (50%), ARLD (25%) and HCV (10%); surveillance adherence in prior year: 2 scans (0%), 1(75%), 0(5%); self-reported barriers (median 2); and no internet access (30%). 7 themes were identified [1] Information and Communication Deficits [2] The Critical Role of Human Interaction in Trust and Clarity [3] Compromised Confidence: Systemic and Technical Barriers to Care Quality [4] Health Literacy and The Varied Interpretation of Diagnostic Results [5] Digital Tools: Limited Adoption and Reliance on Social Scaffolding [6] Confidence in the Pathway: Institutional Trust Versus Informed Belief [7] Multifactorial Drivers of Surveillance Non-Adherence. Analysis revealed a profound deficit in patient understanding regarding the purpose and importance of surveillance, with a substantial proportion (55%) reporting they received no explanation. Patients valued personal interaction over digital tools, relying on direct conversations to build trust and clarify information. Confidence was often undermined by systemic issues, while psychological fears, other health priorities, and logistical challenges reduced participation.

Conclusion:
Improving adherence requires patient-centred pathway redesign. Clear communication, human-led dialogue, and psychological support are essential, alongside practical solutions such as co-locating tests and addressing co-morbidities. Trust and informed engagement, rather than digital tools or logistical fixes, are key to improving adherence and outcomes.

PO4-17
RoI of PIVKA-II as a screening tool for HCC in a occidental cohort.

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Background and aims:
Guidelines advocate the inclusion of cirrhotic patients in surveillance programs for early detection of hepatocellular carcinoma (HCC), utilizing biannual ultrasound and serum alpha-fetoprotein (AFP) assessment. Despite this, the sensitivity for detecting lesions under 2 cm remains below 40%. Consequently, novel biomarkers, such as protein induced by vitamin K absence (PIVKA-II), are of considerable interest due to their potential clinical utility.

Our objective was to assess differences in AFP and PIVKA-II serum concentrations between patients with HCC at BCLC stages 0-A and those with cirrhosis.

Method:
This prospective unicenter study enrolled patients newly diagnosed with HCC alongside cirrhotic patients from the screening program, spanning July 2024 to July 2025. The HCC cohort was restricted to cases with a solitary nodule under 30 mm. According to prior studies from our group, PIVKA-II levels may be falsely elevated by a glomerular filtration rate (GFR) <60 mL/min/1.73m², INR (>1.2), and serum albumin (<35g/L). Patients with these abnormalities were therefore excluded. For each HCC case, four cirrhotic patients served as controls.

Serum AFP and PIVKA-II were quantified using electrochemiluminescence immunoassay (Cobas e801, Roche). Statistical analyses were conducted using Medcalc software.

Results:
The study comprised 55 HCC patients at BCLC-0/A (85.4% male, median age 68.5), with 28 presenting a single nodule <30 mm. Following exclusions for abnormal GFR, INR, or albumin, the final cohort consisted of 15 HCC [mean nodule size 21.6 mm (SD 6.1)] and 60 cirrhotic patients in which next results were found:

The median AFP level was significantly elevated in HCC patients [3.8 ng/mL, Interquartile Range (IQR): 2.4-5.9], compared to the cirrhotic group (2.3 ng/mL, IQR: 2.0-4.7, p<0.001). Additionally, HCC patients exhibited notably higher PIVKA-II levels (64 ng/mL, IQR: 28.6-134.5) versus the cirrhotic group (22.8 ng/mL, IQR: 18.1-40.3, p<0.001). Although PIVKA-II showed a higher AUC than AFP [0.71 (IC= 0.6-0.8) vs. 0.63 (IC=0.6-0.7) respectively], no significant differences were observed (p=0.56).

Conclusion:
Preliminary results indicate that PIVKA-II may be a valuable marker for early-stage HCC diagnosis, potentially enhancing current screening methods. However, further expansion of the study population is necessary to confirm these findings.

ACKNOWLEDGMENTS: We extend our gratitude to Roche Diagnostics® for the complimentary provision of consumables for PIVKA-II determination.

PO5-2
Photon-Counting Detector CT with Iodine Quantification: Improved distinction between bland and neoplastic portal vein thrombosis

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Background and aims:
Neoplastic portal vein thrombosis (PVT) is a critical prognostic factor in hepatocellular carcinoma (HCC), but its differentiation from bland PVT remains difficult. Photon-counting detector CT (PCD-CT) allows iodine density (ID) quantification in every scan. This study evaluated the diagnostic performance of ID in distinguishing bland from neoplastic PVT.

Method:
In this retrospective study, 104 patients with suspected PVT who underwent PCD-CT between 09/2022 and 08/2024 were included. Patients were grouped as follows: (1) HCC with neoplastic PVT, (2) HCC with bland PVT, (3) bland PVT without malignancy, and (4) neoplastic PVT in non-HCC malignancy. ID was measured in the late arterial (LAP) and portal venous phase (PVP) by two independent radiologists and compared to an established CT feature-based score (including vessel infiltration, thrombus extension, and arterial hyperenhancement).

Results:
ID measurements showed excellent inter- and intra-rater agreement (ICC≥0.99). ID was significantly higher in neoplastic PVT in both phases, achieving 100% and 93.1% sensitivity and 95.9% and 100% specificity in LAP and PVP, respectively. In comparison, the feature-based CT score reached 89.7%/86.2% sensitivity and 81.6%/95.5% specificity for thresholds of ≥1/≥2 existing features. In non-HCC malignancies, ID in LAP had a sensitivity of 69.2% and a specificity of 95.9 %, while ID in PVP achieved 92.3% sensitivity and 100% specificity, supporting its diagnostic utility.

Conclusion:
ID derived from PCD-CT reliably differentiates neoplastic from bland PVT in HCC and outperforms conventional CT features. In non-HCC malignancies, ID is particularly accurate in the portal venous phase, supporting its broader clinical utility as imaging biomarker.

PO5-4-YI
Predicting Decompensation in Advanced HCC on Immunotherapy: The ARTE Score

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Background and aims:
Hepatic decompensation is a major complication in patients with advanced hepatocellular carcinoma (aHCC) undergoing Atezolizumab+Bevacizumab (AB). Early identification of high-risk patients is essential to guide management. We aimed to develop a simple score to predict decompensation.

Method:
For this study we enrolled 453 consecutive patients with aHCC treated with immunotherapy from 2020 to 2024, derived from the ARTE database. Inclusion criteria were: AB therapy as 1st line; Child-Pugh ≤A6 cirrhosis without baseline features of decompensation (Baveno-VII). The occurrence of decompensation was recorded, and univariate and multivariate Cox regression analyses were performed to identify predictors. Variables significant in multivariate analysis were used to construct a weighted score based on respective beta coefficient, which was then converted into a simple point-based bedside algorithm. Patients were stratified into low, intermediate, and high-risk groups.

Results:
In the ARTE database, 74 (16.3%) patients developed hepatic decompensation. Median follow-up was 14 months (IQR 7–22). **Neoplastic portal vein thrombosis (HR 1.97, 95% CI 1.20–3.23, p=0.007), elevated bilirubin (HR 2.61, 95% CI 1.52–4.47, p<0.001), and low platelets (HR 1.82, 95% CI 1.07–3.10, p=0.026)** were identified as independent predictors of decompensation. These variables were incorporated into the ARTE-score depending on their weighted beta coefficient value. Patients were categorized as low (0–1 points, n=360), intermediate (2 points, n=49), or high risk (3-4 points, n=44).

Compared with the low-risk group, intermediate-risk patients had a 1.96-fold higher hazard of decompensation (HR 1.96, 95% CI 1.04–3.71, p = 0.038), while high-risk patients had a 4.28-fold higher hazard (HR 4.28, 95% CI 2.41–7.57, p < 0.001). Kaplan–Meier analysis demonstrated significant separation of decompensation-free survival across risk groups (p<0.001). The ARTE-score showed good discrimination for decompensation **(Harrell's C = 0.7022, Somers' D = 0.4045**). Decompensation-free survival at 12 and 24 months was 87% and 83% for low-risk, 79% and 64% for intermediate-risk, and 57% and 56% for high-risk.

Conclusion:
The ARTE score is a simple and effective tool to predict hepatic decompensation in aHCC in AB, improving risk stratification and guide clinical decision-making.

PO5-6
Cabozantinib in recurrent hepatocellular carcinoma after liver transplantation

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Background and aims:
Cabozantinib (CABO), a second- or third-line therapeutic option for hepatocellular carcinoma (HCC), has been shown to improve overall survival (OS) in patients previously treated with sorafenib (SOF) or lenvatinib (LEN) who experience disease progression (PD) or intolerance to first-line tyrosine kinase inhibitors (TKIs). This study aimed to assess the safety and clinical outcomes of CABO used as second- or third-line therapy for recurrent HCC (rHCC) following liver transplantation (LT).

Method:
We conducted a retrospective, multicenter study including LT recipients treated with CABO in second and third line for rHCC. Baseline clinical characteristics and treatment-related outcomes were analyzed.

Results:
Thirty-one LT patients were included (median age 60 years [IQR 38-78], 93.5% male). HCCr at the time of CABO treatment involved both intra- and extra-hepatic sites in 16 patients, extrahepatic sites in 14 and was confined to the liver only in one case. The Median time from LT to CABO initiation was 4 (1–11.3) years. CABO was administered as second-line therapy in 5 patients (4 after SOF, 1 after LEN discontinuation for PD) and as third line in 26 patients (after SOF/regorafenib discontinuation for PD in 3, after LEN/SOF in 22 patients). Overall, median time on SOF and LEV was 3.33 months and 6.55, respectively. During 6.5 (0.5–18.2) months of CABO treatment, the most common adverse events were diarrhea (n=16, G3=6), fatigue (n=7, G3=1), hypertension (n=7), anorexia/weight-loss (n=6) and HFS (n=6; G3=1). Only one case of liver rejection was recorded on CABO, and tacrolimus dose adjustment was required in 4. Twenty patients discontinued CABO due to PD, 5 for other non–treatment-related reasons, and 25 patients died along the period. Median OS from rHCC was 31.5 months (95%CI 21.2–42.2), and from the start of CABO treatment was 11.5 months (95%CI 4.8–17.9).

Conclusion:
This study represents the largest reported cohort describing CABO use after LT, demonstrating an acceptable safety profile and supporting its role in the management of post-transplant HCC recurrence after first line treatments.

PO5-7-YI
MASLD-related hepatocellular carcinoma in cirrhotic and non-cirrhotic patients: a real-world analysis from the ITA.Li.Ca. cohort

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Background and aims:
Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of hepatocellular carcinoma (HCC), which may develop with or without cirrhosis. The study aimed to assess differences in tumour burden, treatment access, and outcomes between cirrhotic and non-cirrhotic MASLD-related HCC.

Method:
Data from the ITA.Li.Ca. database (27 centres, 2003–2022) were retrospectively analysed. Patients with MASLD-related HCC and no other liver disease aetiologies were included. Baseline clinical, biochemical, and tumour features were compared according to cirrhosis status. Tumour response was classified according to mRECIST criteria.

Results:
Among 903 eligible patients, 273 (30%) were non-cirrhotic. Only 25% were under ultrasound surveillance; 64% showed no significant fibrosis by FIB-4. Cirrhotic patients were more often obese and diabetic, with worse liver function (MELD 9.7 vs 8.5; p<0.001). Non-cirrhotic patients had larger tumours (≥50% parenchymal involvement 15% vs 8%; p=0.01) but similar rates of vascular invasion and metastases.Almost half of non-cirrhotic cases lacked histological confirmation despite recommendations.When we separately analysed cirrhotic and non-cirrhotic patients not undergoing surveillance, non-cirrhotic patients had bigger tumours (p value <0,001), although without differences in tumour spread.This difference was also confirmed in patients undergoing semi-annual surveillance (10% vs. 2.6%, p =0.029).In the whole cohort, no significant differences in overall survival were observed between cirrhotic and non-cirrhotic patients, regardless of the treatment they received.Non-cirrhotic patients underwent more resections (64% vs 31%), while cirrhotics received more ablation (27%) and transplantation (15%). Tumour burden remained higher in non-cirrhotics irrespective of surveillance. Overall survival did not differ by cirrhosis status or treatment type (log-rank p>0.05 for all).

Conclusion:
MASLD-related HCC in non-cirrhotic patients presents with greater tumour burden but comparable survival to cirrhotic HCC. Despite guideline recommendations, biopsy is often omitted in non-cirrhotic cases. Treatment selection should prioritise tumour and liver function characteristics rather than the presence of cirrhosis. These findings highlight the need for tailored surveillance strategies in non-cirrhotic MASLD.

PO5-8
Validation and modification of AJCC 8th staging system for Distal Bile Duct Cancer

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Background and aims:
The American Joint Committee on Cancer (AJCC) 8th staging system of distal bile duct cancer was dramatically revised. We attempted to provide validation and suggest potential improvement for the current staging system.

Method:
Distal bile duct cancer patients who underwent radical surgery from January 2018 to December 2023 were retrospectively reviewed. The overall survivals (OS) of each AJCC 8th stage were compared. Revised staging system was developed based on the results of prognostic factor analyses.

Results:
A total of 249 patients were followed up for median 34.5 months (range, 0.1-89.5 months). There was no significant prognostic difference between T2 and T3 ($p = 0.095$), and N1 and N2 ($p = 0.487$). In multivariate analysis, tumor size ≥ 3cm, and portal vein or superior mesenteric vein involvement were independent adverse factors for OS ($p < 0.05$), whereas the depth of tumor invasion lost statistical significance after adjusting for other prognostic factors. In patients with nodal involvement, location of involvement at hepatoduodenal ligament, along common hepatic artery, or along superior mesenteric artery rather than the number of involved lymph nodes was associated with inferior OS. Revised staging system based on these factors showed statistically significant difference for OS ($p < 0.05$).

Conclusion:
Current T- and N-stages failed to show significant prognostic differences in current cohort. In contrast, suggested revised staging system showed excellent performance in discriminating prognostic groups. Novel approach incorporating tumor size and nodal station may lead to improved patient prognosis prediction. Based on the results, we plan to conduct an external validation to generalize the new staging system.

PO5-9-YI

Peripheral Lymphocytes in human liver hepatocellularcarcinoma: a newdruggable target as well as biomarker to help diagnosis and predictimmunotherapy response

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Background and aims:
Hepatocellular carcinoma (HCC) represents the second leading cause of cancer-related death worldwide, deriving mainly from either viral insult (e.g. HBV and HCV), metabolic syndrome (MASLD), eventually associated with chronic alcohol abuse (MetALD), or other causes of chronic liver disease. Over the past decade, immune checkpoint inhibitors (ICI) have revolutionized HCC treatment, adding new therapeutic opportunities for patients with intermediate or advanced disease (as classified by BCLC staging system). However, criteria and guidelines for patient selection are missing and insufficient. Therefore, identifying the immunological signatures in each etiology represents a fundamental step for patient selection and therapeutic decision toward a fullypersonalized medicine approach.

Method:
Patients were systematically categorized into three etiological groups: viral hepatitis (HBV or HCV), metabolic-associated liver disease (MetALD), and metabolic/ex-viral+MASLD conditions. Data preprocessing included KNN imputation (k=5) for missing values and winsorization (0.02-0.05) for out-of-range parameters. Comprehensive statistical analyses were performed using Mann-Whitney tests for pairwise comparisons, Kruskal-Wallis tests for multi-group analysis, and post-hoc Dunn tests for specific group differences. XGBoost machine learning algorithms were employed for etiological discrimination and therapy response prediction using Leave-One-Out Cross-Validation

Results:
Inter-etiological comparisons demonstrated significant differences in NK(%), CD4/CD8 ratio, white blood cells, neutrophils, monocytes. XGBoost classification achieved moderate-to-good discrimination between etiological groups (AUC range: 0.677-0.832). Novel combined immunological-morphological variables showed enhanced discriminatory power: CD8+CD57+(%)/nodule number (p=0.021), NK(%)/nodule number (p=0.006), and NK(%)/largest nodule dimension (p=0.021). For systemic therapy response prediction, the model achieved robust performance (AUC=0.836, precision=0.800, recall=0.727) using CD8+CD57+(%), and IGD+CD27-(%) as primary features

Conclusion:
Lymphocyte profiles demonstrate significant heterogeneity across liver disease etiologies HCC and possess substantial potential for diagnostic discrimination and treatment response prediction, suggesting their clinical utility as immunological biomarkers.

PO5-10
Defining efficacy and dosimetric parameters for yttrium-90 radioembolization in hepatocellular carcinoma: a single-center experience with mRECIST and LI-RADS Radiation TRA in the era of immunotherapy

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Background and aims:
Yttrium-90 transarterial radioembolization (TARE-Y90) for hepatocellular carcinoma (HCC) has evolved with personalized dosimetry and integrated systemic immunotherapies. This study evaluated TARE-Y90 efficacy and safety in a contemporary HCC cohort, assessing concordance between mRECIST and LI-RADS Treatment Response Assessment v2024 (LI-RADS TRA) criteria for response definition, and determining minimal median tumor absorbed dose (TAD) and estimated absorbed dose by 70% of tumor (D70) for radiological response.

Method:
Retrospective analysis of a single-center cohort of HCC patients treated with glass microspheres-Y90 from 2021 to 2025. Data included baseline clinical characteristics, treatment response (mRECIST and LI-RADS Radiation TRA v2024 criteria at 3 months and thereafter), dosimetric variables and follow-up. All therapeutic decisions were made within a multidisciplinary tumor board.

Results:
The cohort comprised 54 patients (93% males), median age 73.8 years. Most (87%) had liver cirrhosis, primarily alcohol-related (52%), followed by Hepatitis C (15%) and MASLD (13%). Liver function showed ALBI-1 in 83% and Child-Pugh A5 in 90.6%. At TARE-Y90, 44.4% were MILAN-IN, 24.1% BCLC-B, and 31.5% BCLC-C. TARE-Y90 was first-line therapy in 81.5%. Vascular approach was radiation segmentectomy for 87% and lobectomy for 13%. Median administered activity was 2.23 GBq, with median TAD of 434 Gy.

Concordance to define response between mRECIST and LI-RADS Radiation TRA v2024 criteria was fair (Kappa = 0.36). In contrast, concordance for defining progression demonstrated substantial agreement (Kappa = 0.91).

Thresholds for total TAD and D70 for mRECIST response were 376 Gy and 282 Gy at 3 months, and 438 Gy and 283 Gy at 6 months, respectively. Median duration of response was 7.67 months. Overall survival rates were 81% at 1 year and 55% at 3 years. Baseline ALBI score significantly associated with survival (HR 6.488, p=0.037).

Conclusion:
TARE-Y90 demonstrates sustained efficacy and safety in HCC, validating specific dosimetric thresholds for radiological response crucial for personalized therapy. While mRECIST and LI-RADS TRA v2024 exhibit fair concordance for response evaluation, their near-perfect agreement for progression assessment highlights distinct clinical utility. Baseline ALBI score is a significant prognosticator, emphasizing liver function's critical role. These findings reinforce TARE-Y90's value and inform optimization strategies in evolving HCC management.

PO5-11-YI
Plasma GDF15, Angiopoietin-2, and miRNAs as diagnostic tools in chronic liver disease progression to HCC

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Background and aims:
Early detection and risk assessment of hepatocellular carcinoma (HCC) remain critical challenges. Circulating biomarkers could enhance differentiation between stages of chronic liver disease (CLD) and identify patients at risk of progressing to cirrhosis and HCC. Among potential biomarkers, growth differentiation factor 15 (GDF15) reflects cellular stress and fibrosis, angiopoietin-2 (Angiop2) indicates abnormal angiogenesis, and microRNAs such as miR-21 (related to inflammation and fibrosis), miR-34 (regulates apoptosis), and miR-122 (signifies hepatocyte function) represent distinct pathogenic processes during disease progression. The study aims to evaluate the diagnostic and prognostic value of circulating GDF15, Angiop2, miR-21, miR-122, and miR-34 across the spectrum of liver disease, focusing on distinguishing cirrhosis/HCC from earlier stages of CLD.

Method:
We retrospectively enrolled 116 subjects: 16 healthy individuals, 34 with CLD, 28 with cirrhosis, and 38 with HCC. Plasma GDF15 and Angiop2 were measured using ELISA according to standard protocols. Circulating miRNAs were isolated using commercial RNA extraction kits and quantified by qRT-PCR. Relative expression was determined using the delta-delta-Ct method, normalized against endogenous reference miRNAs.

Results:
All biomarkers demonstrated significant differences across disease stages. Cirrhosis/HCC patients showed higher levels of GDF15, Angiop2, miR-21, and miR-34, with lower miR-122 compared to CLD patients (all $p < 0.0001$ except Angiop2, $p = 0.017$). Correlations with clinical severity measures were strongest in cirrhotic patients: GDF15 correlated with MELD ($p = 0.002$) and trended with Child-Pugh ($p = 0.169$), while Angiop2 correlated with both MELD ($p < 0.0001$) and Child-Pugh ($p = 0.009$). ROC analysis showed excellent diagnostic accuracy for GDF15 (AUC 0.948) and Angiop2 (AUC 0.937), and good performance for miR-21 (AUC 0.815) and miR-34 (AUC 0.758), all $p < 0.0001$. In the overall cohort, GDF15, Angiop2, and miR-122 significantly correlated with OS ($p < 0.0001$); however, these prognostic links weakened within individual disease subgroups.

Conclusion:
Biomarker profiles clearly distinguish cirrhosis/HCC from CLD. GDF15 and Angiop2 exhibit the best diagnostic performance and, along with microRNAs, may enhance clinical scores for identifying high-risk patients and provide insights into the biological mechanisms behind the transition from CLD to malignant transformation.

PO5-12
Combined hepatic arterial infusion chemotherapy, lenvatinib, anti-PD-1/PD-L1 antibody as conversion therapy for unresectable hepatocellular carcinoma: A 5-year real-world cohort study

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Background and aims:
Conversion therapy is valuable for unresectable HCC, and HAIC + lenvatinib + ICI has an ORR >60% but lacks long-term follow-up data in existing studies. We conducted a study with long-term follow-up to assess this regimen's efficacy, safety, and surgical conversion rate for unresectable HCC.

Method:
This study was a post-hoc analysis of the HAIC-lenvatinib-ICI cohort from CCGLC-001, including unresectable HCC patients who received HAIC-FOLFOX + lenvatinib + anti-PD-1/PD-L1 antibody at 4 centers (3 Tongji Hospital branches, Wuhan; Second Hospital of Fujian Medical University, Quanzhou) since May 2020, and evaluated the treatment's efficacy, safety, and surgical conversion rate.

Results:
In a multicenter study of 226 unresectable HCC patients treated with HAIC-lenvatinib-ICI, the mRECIST ORR reached 68.1% (12.4% CR, 55.7% PR) with 62.4% achieving CRT (met the criteria of radical treatment) eligibility and 46.8% undergoing radical treatment (72.7% resection, 9.1% transplantation, 18.2% ablation). Notably, 2 of 9 patients with extrahepatic metastases underwent conversion resection. Long-term outcomes included a median PFS of 18.5 months and 5-year OS rate of 53.6%. Patients achieving CRT had significantly longer PFS (28.1 vs. 8.2 months, $p<0.001$) and 24-month OS (81.5% vs. 42.8%, $p<0.001$). Radical treatment conferred sustained survival benefits even after adjusting for baseline differences.

Safety was manageable, with 97.8% experiencing TRAEs (85.4% grade 1–2, 12.4% grade 3–4) and no treatment-related deaths. CRT responders had fewer severe toxicities (7.1% vs. 21.3%, $p<0.001$). Perioperative outcomes showed laparoscopic resection in 68.8%, low 30-day mortality, and pathological responses in 27.1% (pCR) and 42.4% (mCR) of resected cases. These findings validate HAIC-lenvatinib-ICI as a promising strategy for achieving durable tumor control and surgical conversion in advanced HCC.

Conclusion:
Combined HAIC, lenvatinib, and anti-PD-1/PD-L1 antibody yields a high surgical conversion rate in unresectable HCC (62.4% CRT eligibility, 46.8% radical treatment), with a median PFS of 18.5 months and favorable long-term survival. Radical treatment significantly improves PFS even after adjusting for baseline differences, and safety is manageable (mostly grade 1–2 toxicities, no treatment-related deaths). These findings validate this regimen as a promising approach for unresectable HCC.

PO5-13-YI

A comparison of MAFLD and MASLD diagnostic criteria in estimating the risk of de novo hepatocellular carcinoma occurrence in HCV patients achieving sustained virological response

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Background and aims:
A higher risk of hepatocellular carcinoma (HCC) has been widely reported in patients with chronic hepatitis C virus (HCV) infection who achieve a sustained virologic response (SVR12) induced by direct-acting antivirals (DAAs), presenting with Steatotic Liver Disease (SLD) and cardiometabolic risk factors (CMRFs) indicative of metabolic dysfunction (MD). Two years after the Delphi consensus, the potential benefits of adopting Metabolic dysfunction-associated Steatotic Liver Disease (MASLD) rather than Metabolic dysfunction-associated Fatty Liver Disease (MAFLD) criteria in defining the disease progression risk remain undefined. The present study compared MASLD and MAFLD criteria in estimating the 5-year risk of de novo HCC occurrence in SLD patients achieving DAAs-induced HCV SVR12.

Method:
The anthropometrical, biochemical, clinical, Liver Stiffness Measurement (LSM), and Controlled Attenuation Parameter (CAP) data stored in the “Luigi Vanvitelli” University Hospital Health Documents Digitization Archive of 751 HCV-SVR12-SLD patients (January 2015 - May 2020) were included. After properly excluding lean individuals (i.e., Body Mass Index < 25 kg/m^2) and patients with other causes of chronic liver damage (n. 101), the MAFLD and MASLD criteria were separately applied, ultimately identifying the following groups: HCV-SVR12-MASLD (n. 163), HCV-SVR12-MASLD/MAFLD (n. 390), and HCV-SVR12-MAFLD (n. 97). HCC occurrence was diagnosed according to the EASL guidelines and retrospectively reported along a 5-year follow-up.

Results:
At baseline, no significant clinical differences emerged among the groups, and a similar distribution of LSM-advanced fibrosis (AF) was reported in HCV-SVR12-MASLD and HCV-SVR12-MAFLD [53 (32.51 %) vs 34 (35.05 %), chi-square, p > 0.05]. Compared to MASLD, MAFLD diagnostic criteria better estimated the risk of HCC [HR: 1.936, C.I. 95%: 1.083 - 2.375, p: 0.035], even after stratifying for AF baseline presence (chi-square, p < 0.0001). Multivariate competing risk analysis (adjusted for sex, age, diabetes, steatosis, SVR achieving time, CAP, and fibrosis severity) revealed diabetes (aHR: 2.051, p: 0.001), high-sensitivity-C-reactive protein (aHR: 1.351; p: 0.02), and Homeostatic-model-assessment-for-insulin-resistance (aHR: 1.219; p: 0.02) as variables significantly associated with this outcome.

Conclusion:
MAFLD criteria better estimate the de novo HCC risk in SLD patients achieving DAAs-induced HCV SVR12.

PO5-14-YI
Adding artificial intelligence support to the multidisciplinary oncologic group-guided decision process is a valid strategy to optimize tailored therapies in the hepatocellular carcinoma management

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Background and aims:
Multidisciplinary discussions within dedicated oncologic boards comprising hepatologists, oncologists, and surgeons (Multidisciplinary Oncologic Group "MOG") represent a routine practice in the management of hepatocellular carcinoma (HCC). In recent years, various artificial intelligence (AI) tools, mainly for predicting therapeutic response, have been developed. However, the contribution of integrating the AI support with the MOG-guided therapeutic planning remains unexplored.

Method:
We consecutively enrolled (December 2019 - October 2022) 88 patients with advanced chronic liver disease (ACLD) who received a new diagnosis of HCC. At enrollment, biochemical, clinical (including ACLD etiology and Child-Pugh score), and cancer-related data (dimensions, vascular invasion, and alpha-fetoprotein levels) were collected, and the Barcelona Clinic Liver Cancer (BCLC) criteria were adopted exclusively to stage the disease progression at diagnosis. According to this, after properly performing stratified randomization, patients were proportionally distributed into two groups: (i-MOG) patients managed following exclusively the MOG-guided decision process (MDG) (n: 43); (ii-MOGAI) patients managed following MGD, subsequently optimized with the support of the open AI tool ChatGPT (v. 5) (n: 45) including: a) the generation of a specific patient-data-based objective prompt; b) the generation of prompt-based outcomes, eventually, followed by a prompt-refinement process; c) the final application with multidisciplinary concorded relative adjustments to the initially performed clinical MGD. Patients were followed up for three years, and the overall survival (OS) and disease-free survival (DFS) were evaluated.

Results:
At baseline, no statistically significant differences and a similar stage at the diagnosis distribution emerged in the comparison between the two groups (MOG vs MOGAI: BCLC-0, A, B: 27.9 % vs 31.1 %, 25.5 % vs 22.2 %, 16.2 % vs 17.8 %, 20.9 % vs 22.2 %, 9.4 % vs 6.7 %; chi-square, $p > 0.05$). The overall rate of concordance between MDG and MOGAI final decision was 81.2 %; refinement was required in 28 % of MOGAI cases. The most frequent treatment in MOG and MOGAI was ablation (39.5 %) and resection (44.4 %), respectively. A significantly increased OS (HR: 0.384; p: 0.04) and DFS (HR: 0.438, p: 0.038) were highlighted in the MOGAI group.

Conclusion:
Integrating AI support is a valid strategy for selecting the most effective therapy in HCC.

PO5-15-YI
Circulating reticulated platelets in hepatocellular carcinoma with and without liver cirrhosis

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Background and aims:
Reticulated platelets (RePLT) are newly released, hyper-reactive platelets reflecting thrombopoietic activity. Their role and activation status in hepatocellular carcinoma (HCC) remains unexplored. This study investigated RePLT alterations and activation patterns in advanced HCC patients with and without underlying liver cirrhosis (LC).

Method:
We prospectively enrolled 55 subjects into four groups: healthy controls (CTRL, n = 28), LC without HCC (LC+ HCC-, n = 13), HCC on a healthy liver (LC- HCC+, n = 7), and HCC on cirrhosis (LC+ HCC+, n = 7). Exclusion criteria included portal vein thrombosis, antiplatelet therapy, and Child-Pugh B/C. Thrombocytopenia was defined as a platelet count less than 150×10³/μL. RePLT and highly-reticulated platelets (top 1% by RNA content – High-RePLT) were quantified by flow cytometry. Platelet activation was assessed using phosphatidylserine and p-selectin before and after thrombin receptor-activating peptide (TRAP) stimulation. A three-way ANOVA evaluated the independent effects of HCC, LC, and thrombocytopenia on the RePLT. The Kruskal-Wallis test assessed differences in platelet activation markers.

Results:
The study groups were comparable for sex, but differed in age and baseline platelet (median [IQR] ×10³/μL: CTRL 196 [163–221], LC+ HCC- 139 [95–162], LC+ HCC+ 87 [80–131], LC- HCC+ 261 [170–280]; p = 0.001). RePLT were significantly lower in HCC patients (median: CTRL 4.0%, LC+ HCC- 4.9%, LC+ HCC+ 1.5%, LC- HCC+ 1.1%; p < 0.001). At the three-way ANOVA, the presence of HCC was associated with a 2.6% lower RePLT percentage (p = 0.004), while LC and thrombocytopenia showed no significant effects. LC- HCC+ showed a significant reduction in phosphatidylserine (median: CTRL 46%, LC+ HCC- 78%, LC+ HCC+ 29%, LC- HCC+ 19%; p < 0.001) and p-selectin (median: CTRL 94%, LC+ HCC- 99%, LC+ HCC+ 35%, LC- HCC+ 17%; p < 0.001) expression in High-RePLT. After TRAP stimulation, LC+ HCC- patients demonstrated reduced phosphatidylserine expression but increased p-selectin compared with all the other groups, while HCC patients did not differ from healthy controls.

Conclusion:
HCC is associated with a reduction in RePLT percentage independent of thrombocytopenia and cirrhosis, together with a lower expression of activation markers, particularly in HCC without cirrhosis. Further studies are warranted to clarify the mechanism and clinical relevance of these findings.

PO5-16-YI
The Role of Atezolizumab and Bevacizumab in Hepatocellular Carcinoma (HCC) with advanced basal tumour burden: from neoplastic portal invasion to extrahepatic metastasis

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Background and aims:
Hepatocellular carcinoma (HCC) with neoplastic portal vein thrombosis (nPVT) and extrahepatic metastases represents a challenging clinical scenario. The combination of atezolizumab and bevacizumab (A+B) has emerged as standard first-line therapy, yet outcomes in patients with advanced tumour burden remain poorly characterised. This study evaluates the efficacy and safety of A+B across different basal patterns of disease extension.

Method:
We conducted a retrospective analysis of 553 patients collected prospectively with advanced HCC from the ARTE registry. Patients were stratified by disease pattern: intrahepatic only, nPVT alone, extrahepatic metastases alone, or combined nPVT with metastases. Primary endpoints included overall survival (OS), progression-free survival (PFS), and response rates. Cox regression models identified independent prognostic factors.

Results:
The cohort comprised 553 patients (median age 72 years, 81.2% male). nPVT was present in 331 patients (59.9%), whilst extrahepatic metastases occurred in 185 patients (33.5%). Median OS was 21 months (95% CI: 18.2-23.8), with significant differences by disease pattern (p=0.01): intrahepatic only 27 months, nPVT alone 22 months, metastases alone 18 months, and combined pattern 15.5 months. Disease control rate (DCR) was achieved in 389 patients (72.7%), with significant variation by pattern (p=0.0002). Multivariate analysis identified ECOG performance status (HR 1.6, p<0.001), ALBI score 2-3 (HR 1.2, p=0.026), and log AFP (HR 1.1, p=0.002) but not basal tumour burden pattern as independent predictors of survival.

Conclusion:
A+B demonstrates differential efficacy across HCC disease patterns. Patients with intrahepatic disease achieve superior outcomes, whilst those with combined vascular invasion and extrahepatic spread have the poorest prognosis. However, liver function and performance status are the major driver of OS. These findings support pattern-based prognostic stratification in clinical decision-making

PO5-17-YI
Real-world compliance with hepatocellular carcinoma surveillance: experience from a regional service

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Background and aims:

Adherence to HCC surveillance programmes remains variable in real-world settings. We evaluated compliance within our regional cohort of patients with liver disease.

Method:

Retrospective analysis was conducted of 751 patients enrolled in a hepatocellular carcinoma (HCC) surveillance programme between 2006 to 2019. This is a prospectively managed database maintained and updated through to 2025. Data was extracted from electronic patient records where we audited 6-monthly ultrasound surveillance, endoscopic variceal screening, and bone density assessment. Expected vs completed ultrasound scans were compared to assess compliance.

Results:
Of 716 patients, the median number of ultrasound scans performed per patient was 12.2, over a median follow-up of 5.8 years. Overall mean compliance with recommended 6-monthly intervals was 63.3% (n = 453). Cirrhotic patients were more likely to be compliant (65.6%, n = 411) than non-cirrhotic patients (46.9%, n = 42). Amongst cirrhotic patients, 70.4% (n = 504) and 70.3% (n = 503) underwent endoscopy and DEXA scanning, respectively. Overall, HCC surveillance protocol was followed 74.9% (n = 536) of the time and 21.8% (n = 156) of patients were lost to follow-up.

Conclusion:
Here we demonstrate suboptimal compliance with HCC surveillance, where over one-third of patients are missing scheduled ultrasound appointments. Cirrhotic patients had higher adherence rates than non-cirrhotic patients, but additional guideline screening for varices and osteoporosis could be improved. Improved surveillance pathways and recall systems may improve HCC surveillance adherence and facilitate earlier detection of HCC.

PO6-1-YI
Prognostic value of KRAS and TP53 mutations in patients with advanced biliary tract cancer treated with chemo-immunotherapy

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Background and aims:
Cisplatin, gemcitabine and durvalumab has emerged as a frontline treatment for advanced biliary tract cancer (BTC), however predictors of response are still lacking. The immunogenomic heterogeneity of BTC presents both challenges and opportunities for personalized immunotherapy. *KRAS* and *TP53* mutations could correlate with an aggressive tumor microenvironment. Our study aims to identify genetic markers associated with outcomes.

Method:
This observational study included 38 patients (pts) with BTC treated with first-line cisplatin, gemcitabine and durvalumab between April 2022 and October 2025 at a single tertiary center. Molecular profiling performed using next-generation sequencing was available for all pts evaluated. Association between *KRAS* and *TP53* mutational status and disease control rate (DCR) was analyzed using Fisher's exact test. Differences in survival between groups were assessed using log-rank test. A two-sided p-value < 0.05 was considered statistically significant.

Results:
Among 38 pts, 6 (15.8%) had a *KRAS* mutation: *KRAS* G12D (50%), *KRAS* G12R (16.7%) and *KRAS* G12V (33.3%). *TP53* mutations were found in 8 pts (21%). Two pts (5%) had both mutations. Pts were divided into two subgroups based on best overall radiological response within 6 months (range 1–6 months) from treatment start: those with disease control including stable disease or partial or complete response (29, 76.3%) and those with progressive disease (9, 23.7%). A trend toward a higher DCR among pts with *KRAS* wild-type (WT) tumors compared with mutant (81.25% vs. 50%; p = 0.13) was shown. *TP53* mutation status seemed not to have an impact on DCR, as the rates were similar between the two groups (87.5% vs. 73.3%; p = 0.65). Pts with *KRAS*-mutant tumors had a shorter overall survival (OS) than WT (7.2 vs. 12.0 months; p = 0.07). Progression-free survival (PFS) was shorter in pts with *KRAS*-mutant tumors (2.3 vs. 7.4 months; p = 0.02). Pts with *TP53* mutations showed shorter OS than WT (10.29 vs. 11.67 months; p = 0.82), while no difference was observed in PFS (7.40 vs. 7.07 months; p = 0.38).

Conclusion:
In our study *KRAS* and *TP53* mutations showed a trend toward shorter OS compared with WT tumors, although this difference was not statistically significant. While validation in a larger cohort is necessary, these findings highlight the potential prognostic role of molecular profiling.

PO6-2-YI

The multifaced role of post-operative serum phosphate level in the development of post-hepatectomy liver failure: a prospective preliminary analysis

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Background and aims:
Post-hepatectomy hypophosphatemia (PHH) has been linked to increased metabolic demands. Some authors associate PHH with liver regeneration, while others interpret it as metabolic exhaustion leading to post-hepatectomy liver failure (PHLF). This study aims to explore the serum phosphate dynamics and their association with PHLF and post-operative liver regeneration.

Method:
Consecutive patients undergoing hepatic resection for primary or secondary liver tumors at a single institution (July 2023–July 2024) were prospectively enrolled. PHLF was defined according to the International Study Group of Liver Surgery (ISGLS) criteria. Serum phosphate levels and clinical-biochemical parameters were recorded. Generalized Additive Models (GAMs) explored the relationship between postoperative phosphate drop and PHLF, both univariately and after adjusting for other established a priori predictors. Liver regeneration was assessed in a subgroup using the degree of hypertrophy (DH).

Results:
Among 160 enrolled patients, 29 (18.1%) developed PHLF. All experienced a significant postoperative phosphate decrease, reaching a nadir at postoperative day (POD) 3. PHLF patients showed a significantly greater phosphate drop at POD3 than non-PHLF patients (47.3% vs 21.4%, $p<0.001$). Non-PHLF patients recovered baseline phosphate by POD5, whereas PHLF patients did not ($p<0.001$). Univariate GAM demonstrated a significant, non-linear J-shaped association between POD3 phosphate drop and PHLF risk ($p<0.001$). This relationship persisted as an independent predictor in the multivariate model (edf=2.58, $\chi^2=12.28$, $p=0.009$), together with higher preoperative bilirubin and future liver remnant <50% ($p<0.05$ for both). The non-linear model outperformed the linear one ($p=0.035$). In a subgroup analysis (n=26), a greater phosphate drop at POD3 correlated with higher DH (77.9% vs 49.5%, $p=0.038$), despite similar baseline elastographic characteristics and PHLF incidence.

Conclusion:
Post-hepatectomy phosphate dynamics exhibit a dual behavior. A moderate decline indicates adaptive regeneration and minimal PHLF risk, while excessive drops associate with higher PHLF probability. These findings may resolve discrepant literature evidence opening to PHH as a potential early diagnostic biomarker and therapeutic target for optimizing postoperative liver function.

PO6-3-YI
Long-term outcomes and decompensation events in patients enrolled in hepatocellular carcinoma surveillance

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Background and aims:
Long-term outcomes of patients enrolled in hepatocellular carcinoma (HCC) surveillance programmes remain poorly characterised. We aim to describe the demographics, decompensation rates, and outcomes of patients under a structured HCC surveillance programme at our regional tertiary centre.

Method:
Retrospective analysis was conducted of 751 patients enrolled in an HCC surveillance programme between 2006 to 2019. This is a prospectively maintained database updated through to 2025. Data was extracted from electronic patient records recording demographics, decompensation events, and mortality data. Median follow up was calculated from first scan to last contact or date of death.

Results:
Of 751 patients, the median age was 53 years (SD ± 11.3), where 63.2% (n = 475) were male. Cirrhosis was confirmed in 87.6% (n = 658). Common aetiologies included alcohol-related liver disease (37.8%, n = 284), viral hepatitis (32.4%, n = 243), and metabolic dysfunction-associated liver disease (9.19%, n = 69). Median overall follow up was 5.39 years. During follow up, 38.2% (n = 287) developed varices and 39.7% (n = 298) decompensated: ascites (34.8%, n = 261), variceal bleed (11.3%, n = 85), spontaneous bacterial peritonitis (4.66%, n = 35), and hepatic encephalopathy (11.2%, n = 84). HCC occurred in 12.1% (n = 91) of patients, with a mean time of 4.74 years from first scan to diagnosis. Annual incidence of HCC increased over time. Overall mortality was 45.5% (n = 342) of which 73.6% (n = 67) developed HCC. The average age of death was 63 years (SD ± 10.3). Only 37.3% (n = 280) of patients were considered realistic orthotopic liver transplant (OLT) candidates, of which 12.1% (n = 34) underwent OLT. Median time to first decompensation event was 3.36 years.

Conclusion:
Most patients had cirrhosis and nearly two-fifths of patients experienced a decompensation event. HCC nearly accounted for three-quarters of deaths, highlighting the need for optimised surveillance adherence and early referral for therapy.

PO6-04
Trends in hepatocellular carcinoma (HCC) incidence and impact of hepatitis C antiviral therapy: A population-based subgroup analysis

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Background and aims:
Hepatitis C is one of the most common causes of hepatocellular cancer (HCC) in the United States. Since their introduction in the last decade, direct-acting antivirals (DAAs) have transformed the treatment of hepatitis C, leading to cure rates of over 90% sustained virologic response (SVR). This study explored recent trends in HCC incidence across the U.S, assessing the impact of HCV therapy and subgroup variations by age, race/ethnicity, and sex.

Method:
SEER data from 2014 to 2024 were used to identify adults diagnosed with primary HCC. Inclusion criteria required a confirmed HCC diagnosis and complete demographic information. Patients with metastatic liver cancers or missing key variables were excluded. Age-adjusted incidence rates were calculated per 100,000 person-years. Joinpoint regression was used to estimate the annual percent change (APC) in incidence over time. Subgroup analyses were performed by age group (45–54, 55–64, ≥65), race/ethnicity (White, Black, Hispanic, Asian), and sex. In addition, a real-world cohort of 1,075 patients with hepatitis C virus (HCV) infection who were treated with direct-acting antivirals (DAAs) between 2015 and 2019 was analyzed to assess 5-year post-treatment HCC incidence through 2024.

Results:
From 2014 to 2024, hepatocellular carcinoma (HCC) incidence declined from 11.5 to 9.4 per 100,000 in the U.S. Sub group analysis revealed, 1) by age: 45–54 years (APC –8.22%), 55–64 years (APC –7.03%); 2) by race: Black (APC –10.64%), Hispanic (APC –8.25%), Asian (APC –8.06%); 3) by sex: male (APC –7.28%), female (APC –2.4%). The sharpest drops were seen in adults aged 45–64 and among Black, Hispanic, and Asian populations. Men had a greater decline than women. While early-stage HCC decreased significantly, advanced-stage cases plateaued or slightly increased in older adults and non-Hispanic Whites.

The highest risk was seen in patients with cirrhosis (2.31/100 PY). Cirrhosis, non-SVR, and baseline liver nodules were significant predictors of HCC.

Conclusion:
HCC incidence has declined, particularly among middle-aged adults and minority populations, reflecting improved HCV treatment uptake. However, disparities persist, women and older adults saw smaller declines and more advanced-stage disease. Post-SVR HCC risk remains elevated in cirrhotic patients, highlighting the need for ongoing surveillance and targeted screening strategies. Expanding early HCV treatment and addressing demographic gaps are essential to further reduce HCC burden.

PO6-11
Challenges in recruiting patients (pts) to clinical trials of systemic therapy in advanced hepatocellular carcinoma (HCC)

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Background and aims:
Despite advances in systemic therapy of pts with HCC, overall survival (OS) remains disappointing and novel therapies are urgently required. Most pts with HCC have multiple co-morbidities, including chronic liver disease, and likely other challenges to clinical trial recruitment. We determined the barriers to recruiting pts to a trial of a novel immunotherapy regimen and whether trial pts represent real-world pts.

Method:
With Caldicott Guardian approval, we retrospectively analysed records of pts approached at a single (lead) centre (Glasgow; July 2022–Sept 2025) for participation in a phase I/II study of AZD5069 in combination with durvalumab in pts with HCC (EudraCT 2020-003346-36). Data included demographics, chronic liver disease, tumour characteristics, barriers to recruitment, subsequent treatments and OS.

Results:
101 pts were approached, 11 (11%) entered the trial. 90 pts (82 male, 8 female), median age = 70 years (range 39-86), median deprivation index = 4 (1=most, 10=least deprived), were excluded and analysed here. 67 (of 90; 75%) had a history or radiological features of cirrhosis, most common risk factors being alcohol (n=*57*; 63%), Metabolic Associated Steatotic Liver Disease (MASLD) (*n=32;* 36%) and a history of hepatitis B or C infection (*n-19*, 21%). Tumour features included multi-focal disease (*n=73*; 81%), macroscopic vascular involvement (*n=36*; 40%), extrahepatic disease (*n=26*; 29%).
27 pts declined participation, 6 were excluded as no trial slot was imminently available (dose escalation cohorts). Pts were ineligible for the clinical trial due to $\geq$ 1 of Child-Pugh B disease (*n=13*), significantly elevated transaminases (*n=3*), platelets <75 x 10^9/L (*n=3*), prolonged QTc (*n=2*), other co-morbidities (*n=10*) or performance status $\geq$ 2 (*n=8*). Tumour was not accessible or high risk for mandatory biopsy (*n=5*) and there was no histological confirmation of HCC on study biopsy in 5 further pts. 74 (of 90; 82%) received non-trial systemic therapy, most commonly atezolizumab + bevacizumab (*n=43*). 61 of 90 pts are deceased, median OS from study approach = 9 months.

Conclusion:
Only 11% of HCC pts approached entered this clinical trial, 27% declined to participate, 10% were ineligible due to requirement for biopsy +/- histological diagnosis. These data have implications for clinical trial design and patient eligibility criteria to make clinical trials more inclusive and representative of real-world pts.

PO6-12
Serum TGF-β1 and IDO1 kinetics for the prediction of clinical outcomes among first-line immunotherapy treated patients with hepatocellular carcinoma

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Background and aims:
Though serum immunosuppressive cytokines, such as TGF-β1 and IDO1, play an important role in cancer immunity and patient prognosis, they have been rarely studied as prognostic biomarkers in immunotherapy-treated hepatocellular carcinoma (HCC) patients. The aim of our study was to evaluate the correlation of baseline and on-treatment values of TGF-β1/IDO1 with overall survival (OS) and progression-free survival (PFS) in HCC patients treated with 1st line atezolizumab-bevacizumab (A/B) or tremelimumab-durvalumab (STRIDE).

Method:
We retrospectively evaluated 86 immunotherapy-treated HCC patients. The baseline characteristics of all patients were evaluated and baseline and sequential (2 and 4 months of treatment) serum TGF-β1/IDO1 were measured. We compared baseline TGF-β1 and IDO1 median levels according to patients' baseline characteristics and studied their correlation with OS/PFS. We also studied the correlation of the on-treatment change of these values from baseline with OS/PFS.

Results:
Patients with cirrhosis and diabetes had significantly lower baseline TGF-β1 (p=0.007 and p=0.039, respectively), as had patients without extrahepatic disease (p=0,03) and within up-to-7 criteria (p=0.002). There was no difference in OS/PFS between patients with low/high baseline TGF-β1, when median was used as cut-off. Patients who had increased serum TGF-β1 in 2 and 4 months compared to baseline had statistically significantly better OS than those with decreased values (29 vs. 12 months, p=0.023 and 41 vs. 14 months, p=0.04, respectively). Patients without progressive disease (PD, p=0.01) had significantly higher baseline serum IDO1 levels than those with PD, as had those with objective response (OR, p=0.049) compared to those without OR and patients within up-to-7 criteria (p=0.05), compared to those exceeding up-to-7 criteria. Baseline IDO1 was significantly correlated with PFS after multivariate analysis (p=0.015, HR=0.615), but not with OS. Patients with higher baseline IDO1 had significantly better OS than those with lower baseline levels, when median was used as cut-off (17.6 vs. 14.6 months, respectively, p=0.046). No correlation of IDO1 change in 2 or 4 months of treatment with OS/PFS was observed.

Conclusion:
On-treatment rises in serum TGF-β1 and higher baseline IDO1 emerge as accessible biomarkers for risk stratification and treatment monitoring in first-line A/B or STRIDE-treated HCC patients, a finding that needs prospective validation.

PO6-13
Liver stiffness and spleen stiffness can predict cirrhosis decompensation after transarterial chemoembolization for hepatocellular carcinoma

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Background and aims:
Local interventional procedures for hepatocellular carcinoma (HCC) may determine cirrhosis decompensation in case of increased loss of liver parenchyma. While new techniques for transarterial chemoembolization (TACE) allow ultra-selective procedures, these may not always be feasible, depending on the location of HCC and anatomy of the patient, as well as baseline liver function. Revealing risk factors for decompensation may allow for a better selection and monitorization of HCC patients. This study aims to determine if liver and spleen stiffness may predict decompensation after TACE.

Method:
We prospectively evaluated 184 patients with compensated cirrhosis and a single HCC nodule who underwent TACE during Jan 2024- Jan 2025. Liver stiffness (LS) and spleen stiffness (SS) were determined before the procedure using Fibroscan®.

Results:
Mean age in the study group was 59.43 +/- 18.45 years, with a predominance of the male gender (55.9%). Etiology for underlying liver disease was viral hepatitis (79 HBV patients, 68 HCV infected patients and 22 HBV and HVD patients) and steatotic liver disease (15 patients). All patients had compensated liver cirrhosis (Child Pugh A), without history of decompensation. 21 patients (11.4%) developed decompensation after TACE. We found statistically significant differences in LS and SS in patients with and without decompensation (31.8 +/- 13.7 kPa versus 20.4 +/- 7.1 KPa, p= 0.03 and 45.8 +/- 12.3 KPa versus 33.9 +/- 10.7 KPa, p= 0.04 respectively). Furthermore, LS over 25 KPa is associated with increased risk of cirrhosis decompensation (RR= 1.78, 1.32-2.09, p= 0.03), as is SS over 45 KPa (RR= 1.52, 1.27-1.74, p= 0.01).

Conclusion:
LS and SS can be used as predictor for hepatic decompensation after TACE in patients with compensated cirrhosis. This may be helpful in determining the best therapeutic procedure for each patient, as well as in stratifying access to therapy.

PO6-14
Conversion surgery after immunotherapy in hepatocellular carcinoma: A French multicentric retrospective study

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Background and aims:
Hepatocellular carcinoma (HCC) is often diagnosed at an advanced stage, precluding upfront resection. Immunotherapy has profoundly changed the management of unresectable HCC, offering high tumour response rates and enabling potential conversion to surgery. However, multicentric data on perioperative safety and survival outcomes after resection in this setting remain limited.

Method:
A multicentric retrospective study was conducted across eight French University Hospitals between 2019 and 2024. Patients initially deemed unresectable who received immunotherapy followed by surgery after achieving a radiologic tumour response were included. Primary endpoints were overall survival (OS) and disease-free survival (DFS). Secondary endpoints included postoperative morbidity (Clavien ≥ III), 90-day mortality, and pathological response.

Results:
Twenty-five patients were included (84% male; median age 59 years; median BMI 25.6 Kg/m^2). Before treatment, 56% were classified as BCLC stage C (VP4 n = 2, VP3 n = 5, VP2 n = 6, nodal metastases n = 2), and 8% as Child-Pugh B7. The median size of the largest lesion was 87 mm (range 57 – 101), with a median number of 3.5 nodules. All patients received a median of 11 cycles of immunotherapy (range 6 – 18) before surgery. An objective partial response was achieved in all cases, with a tumour size reduction in 76% of cases. After immunotherapy, 35% of patients were reclassified as BCLC A, 39% as BCLC C, and liver function remained preserved in all but one case (Child-Pugh B7). A right hepatectomy was performed in 14 patients (56%). The overall rate of major complications (Clavien ≥ III) was 16%, with no 90-day mortality. Median hospital stay was 7 days, including a median of 2.6 days in intensive care. Complete tumour necrosis (100%) was observed in 9 patients (36%). The estimated OS was 96% at 3 months, 91% at 12 months, 81% at 24 months, and remained 81% at 60 months. DFS rates were 100% at 3 months, 95% at 12 months, 75% at 24 months, 58% at 60 months.

Conclusion:
Conversion surgery after systemic immunotherapy for initially unresectable HCC is feasible and safe in experienced centres, showing low postoperative morbidity and favourable 2-year survival outcomes. These findings support the curative potential of hepatic resection following combined immunotherapy and support the need for larger comparative studies to validate its long-term benefit.

PO6-15-YI
Epidemiology and factors affecting survival of intrahepatic cholangiocarcinoma: A population-based study of 12,138 patients

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Background and aims:

Intrahepatic cholangiocarcinoma (ICC) is a rare malignant neoplasm, characterised by its aggressive nature and poor prognosis. Mortality remains high with limited curative options.

Previous studies report increasing incidence of ICC up to 2017 when compared to extrahepatic cholangiocarcinoma. This retrospective study aims to determine the recent trends in the epidemiology of ICC from 2011 to 2022 and the factors affecting the overall survival (OS) of patients with ICC.

Method:
A total of 12,138 patients with ICC diagnosed between 2011 and 2022 were extracted from the American Surveillance, Epidemiology, and End Results (SEER) database using ICD-10 anatomy code C22.1 and ICD-O-3 morphology code 8160/3. Incidence trends were examined. Kaplan-Meier (KM) plots were generated for the cohort and categorical variables. Univariable and multivariable Cox regression were performed, generating hazard ratios (HR) and confidence intervals (CI).

Results:
The incidence of liver cholangiocarcinoma has significantly increased from 165 patients/100,000 in 2011 to 465 patients/100,000 in 2022. The incidence of stage 4 is decreasing, and the incidence of stage 1 is increasing from 2011 to 2022. Most patients were male (50.9%) with a median age of 67 years and the majority lived in metropolitan areas (90.1%). The most common TNM stage is stage 4 (50%). Only 19.4% of patients underwent resection, with 0.8% having total resection with liver transplant. Most patients did not receive radiotherapy (85.3%), while a majority received chemotherapy (57.3%).

Overall survival at 12, 36, 60 and 120 months were 42.0%, 17.1%, 10.8% and 5.7%, respectively. Multivariable Cox regression showed that advanced age (HR 1.01), male sex (HR 1.19), patients who lived in non-metropolitan areas (HR 1.11), advanced TNM stage and patients who did not undergo surgery (HR 3.41) were statistically associated with worse overall survival ($p<0.05$). However, patients who received radiotherapy (HR 0.60) or chemotherapy (HR 0.38) were statistically associated with higher overall survival ($p<0.05$).

Conclusion:
The incidence of ICC has almost tripled from 2011 to 2022, possibly due to increasing investigations. Further research is needed to explain this significant increase in incidence. ICC has poor OS, which is associated with advanced age, male sex, living in non-metropolitan areas (despite increasing incidence in metropolitan areas), and advanced stage. Undergoing surgery, receiving radiotherapy or chemotherapy are associated with higher OS.

PO6-16-YI
18F-Fluorodeoxyglucose positron emission tomography is a predictive factor of early response to atezolizumab-bevacizumab in patients with hepatocellular carcinoma

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Background and aims:
The role of ^{18}F-fluorodeoxyglucose (FDG) or ^{18}F-fluorocholine (FCH) positron emission tomography (PET)/computed tomography (CT) in assessing immunotherapy (IT) response in hepatocellular carcinoma (HCC) remains unclear. This study evaluated the prognostic role of dual-tracer ^{18}F-FDG and ^{18}F-FCH PET/CT or magnetic resonance imaging (MRI) in predicting early response and overall survival (OS) in HCC patients treated with Atezolizumab/Bevacizumab.

Method:
Forty-one patients (37 males; median age 65 years) with unresectable HCC undergoing baseline ^{18}F-FDG and ^{18}F-FCH PET/CT or MRI before IT at Henri Mondor University Hospital (Créteil, France) were analysed. Early response was evaluated after three IT cycles using RECIST 1.1/mRECIST criteria, and defined as disease control rate (DCR), including complete/partial response and stable disease. Metabolic parameters were correlated with DCR, progression-free survival (PFS), and OS.

Results:
Thirty-two patients (78%) had BCLC-C stage (41.5% with macrovascular invasion, 43.9% with metastasis). HCC was multinodular in 30 cases (73.2%), with a median size of the largest lesion of 38 mm (21-86). Early objective response rate was 39%, DCR 66%, and early progression (e-PD) 22%. FDG-PET was performed in 19 patients (46.3%), FCH-PET in 6 (14.6%), and both tracers in 16 (39%). FDG-positive HCC (uptake higher than non-tumoral liver) was observed in 68.6% (median SUVmax 4.8), while extrahepatic FDG uptake in lymph nodes (14.7%; SUVmax 10), portal vein (11.8%; SUVmax 9.1), lungs (11.8%; SUVmax 6.9). FCH-positive uptake was seen in 11 cases (50%; median SUVmax 11.2), and extrahepatic in lymph nodes (22.7%; SUVmax 8.5) and bones (9.1%; SUVmax 24.4). Patients with DCR had fewer FDG-positive HCCs (55% vs 92%, $p = 0.05$) than ePD. FDG-positive HCC correlated with ePD ($p = 0.05$) and shorter OS (8.7 vs 31.7 months, $p = 0.05$). Higher FCH tumour-to-liver ratio (TLR) was associated with death ($p = 0.04$). In univariate Cox analysis, AFP ($p = 0.02$), MELD ($p = 0.01$), ALBI grade >1 ($p = 0.02$), ECOG ≥1 ($p = 0.01$), FDG-positive HCC ($p = 0.05$), and absence of early DCR ($p < 0.001$) predicted poorer OS. In multivariate analysis, ALBI >1 (HR 5.77, 95%CI 1.69-19.7, $p = 0.005$) and DCR (HR 0.33, 95%CI 0.14-0.79, $p = 0.01$) remained independent predictors.

Conclusion:
FDG-positive HCC was associated with ePD and shorter OS in patients treated with Atezolizumab/Bevacizumab, suggesting that baseline metabolic phenotype on FDG-PET may reflect tumour aggressiveness and early IT resistance.

PO6-17-YI
Malnutrition assessed by Systemic Immune-inflammation Index predicts mortality in patients with hepatocellular carcinoma treated with immunotherapy

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Background and aims:
Patients with hepatocellular carcinoma (HCC) are burdened by a risk of developing malnutrition estimated between 65-90%. This condition has been associated with worse survival outcomes in patients with cirrhosis undergoing liver resection or locoregional treatment for HCC. However, the prevalence and impact of malnutrition in patients with unresectable HCC (uHCC) candidate to immune-based therapy (IO) have not been fully elucidated.
In the present study we evaluated the nutritional status in patients with compensated cirrhosis and uHCC starting IO, using clinical scores based on routine blood parameters (Controlling Nutritional Status-CONUT; Prognostic Nutritional Index-PNI; Systemic Immune-inflammation Index-SII) and explored their impact on overall survival (OS).

Method:
We conducted a monocentric retrospective study including 78 consecutive patients treated with IO for uHCC. Nutritional scores were evaluated on blood samples collected before starting IO. Kaplan Meier analysis was performed to estimate OS according to nutritional scores and Cox uni/multivariable regression models were used to identify predictors of survival.

Results:
Patients were mostly males (79%), with median age 68 years (IQR 61-76), median BMI 25.3 kg/m^2 (IQR 23.4- 28.3), with compensated cirrhosis without ascites (77% viral aetiology; 78% with varices). All patients were diagnosed with uHCC (including 24% BCLC B, 76% C; 22% with neoplastic portal vein thrombosis (nPVT)) and were treated with immunotherapy (81% atezolizumab-bevacizumab, 19% durvalumab-tremelimumab).
In our cohort, patients were considered "high risk" for malnutrition: 15% according to SII (>752 ×10^9), 15% to CONUT (≥5) and 65% to PNI (<50).
Patients classified as at high-risk according to SII showed a significantly lower OS (6 (IQR 4-15) vs 22 (IQR 10-31) months, p<0.002).
SII>752×10^9 was an independent predictor of mortality in patients with IO (HR 3.86, 95% CI 1.82-8.23; p<0.001), together with the presence of nPVT and oesophageal/gastric varices, by multivariable Cox regression analysis.

Conclusion:
Malnutrition estimated by SII predicted mortality of patients undergoing IO for uHCC in compensated cirrhosis.
However, the estimation of malnutrition prevalence was not unequivocal across the three scores. Therefore, the development of tailored tools for nutritional assessment for these patients is warranted.

PO7-3-YI

Longitudinal evaluation of neutrophil-to-lymphocyte ratio (NLR) as a prognostic biomarker in patients with hepatocellular carcinoma (HCC) treated with atezolizumab-bevacizumab

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Background and aims:
The neutrophil-to-lymphocyte ratio (NLR) is a widely recognized marker of systemic inflammation and has been increasingly investigated in oncology. This study aimed to assess longitudinal changes in NLR and their prognostic value in patients with unresectable hepatocellular carcinoma (uHCC) treated with atezolizumab plus bevacizumab.

Method:
A retrospective analysis was conducted on 108 patients receiving atezolizumab-bevacizumab as first-line treatment for uHCC. NLR values were calculated at baseline and before each treatment cycle, in parallel with scheduled radiological assessments. Temporal variations in NLR were analyzed according to radiological response, distinguishing patients with disease progression from those achieving disease control.

Results:
A baseline NLR ≥ 3 was associated with poorer outcomes, including a significantly lower overall survival (14.4 vs 28.9 months) and a distinct distribution of response categories compared with patients with NLR < 3. Across the cohort, an increase in NLR >20% from baseline at any time during follow-up was associated with a higher risk of radiological progression (HR 2.50, 95% CI 1.37-4.56). Notably, patients who eventually developed progression showed an early rise in NLR as early as the third infusion, while those with stable disease or objective response maintained steady values. This increase preceded radiological progression by approximately three weeks, suggesting that early NLR elevation may serve as a dynamic marker of impending therapeutic failure.

Conclusion:
NLR represents a relevant prognostic biomarker in patients with HCC treated with atezolizumab–bevacizumab. An early increase in NLR during treatment may anticipate radiological progression, providing a simple and cost-effective tool for real-time monitoring of treatment response.

PO7-4
Multidisciplinary clinic approach improves immunotherapy treatment outcomes in unresectable hepatocellular carcinoma: a multicentre retrospective study

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Background and aims:
Given the complexity of managing unresectable hepatocellular carcinoma (HCC), few Italian centres have implemented integrated multidisciplinary clinics (MDTc), where hepatologists and oncologists jointly assess patients. This study aimed to evaluate whether this model improves survival outcomes in patients treated with Atezolizumab and Bevacizumab (A+B).

Method:
In this multicentre retrospective study, 146 patients with cirrhosis and unresectable HCC treated with A+B were included. Based on the outpatient care model, centres were categorised into two groups: those with MDTc and those with standard oncology clinics, where hepatologists were consulted on demand. Primary outcomes were overall survival (OS) and progression-free survival (PFS); secondary outcomes included disease control rate (DCR) and objective response rate (ORR).
An inverse probability weighting (IPW) analysis was performed to adjust for baseline imbalances between groups.

Results:
Seventy-seven patients (53%) were managed in MDTc settings, and 69 (47%) in oncology clinics. Median treatment duration was 6.0 months (IQR 2.0–11.0). Median OS did not significantly differ between groups [19.7 months (95%CI: 16.6–23.1) vs 13.4 months (95%CI: 10.7–19.5); p=0.07], whereas median PFS was significantly longer in the MDTc group [13.6 months (95%CI: 8.9–NA) vs 7.7 months (95%CI: 4.9–13.0); p=0.02]. While ORR was similar, DCR was higher in the MDTc group (70.1% vs 60.3%; p=0.05). Patients followed in MDTc remained on first-line therapy significantly longer [8 months (IQR 3–12) vs 4 months (IQR 1–8); p=0.009]. Although the overall treatment discontinuation rate did not differ between the two groups, liver-related events were more frequent and accounted for a greater proportion of discontinuations in oncology clinics (40.6% vs 10.4%; p=0.04). Furthermore, treatment duration was shorter in patients discontinuing A+B due to liver-related events than other causes [2.5 months (IQR 1.8–6.3) vs 7.1 months (IQR 3.9–11.2); p<0.001]. However, in the IPW analysis, the association between MDTc management and clinical outcomes was no longer significant.

Conclusion:
In patients with unresectable HCC treated with A+B, MDTc management did not significantly improved OS, but was associated with better PFS and DCR. These benefits were likely driven by longer treatment duration and lower rates of liver-related decompensation, underscoring the value of integrated hepatologic-oncologic management in this complex population.

PO7-5-YI

Clinical features and outcomes of patients with biliary tract cancer and a history of prior tumors: a retrospective cohort study from a tertiary cancer center

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Background and aims:
Biliary tract cancer (BTC) is an aggressive malignancy with poor prognosis. As its incidence increases with age, a proportion of patients in clinical practice present with a history of prior malignancy. However, this subgroup remains underexplored, largely because such patients are typically excluded from clinical trials. We aimed to evaluate clinical features and outcomes of patients with BTC and a history of prior tumor.

Method:
We retrospectively analyzed data from patients with BTC treated at IRCCS Humanitas Research Hospital between 2019 and 2025. Patients were stratified according to the presence or absence of a prior tumor. Associations between prior tumor history and BTC clinico-pathological characteristics and molecular targets were assessed using Fisher's exact test or Chi-square test. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method and compared with the log-rank test. Statistical significance was set as $p<0.05$.

Results:
Of 253 patients with BTC, 40 (16%) (77.5% intrahepatic cholangiocarcinoma, 17.5% extrahepatic cholangiocarcinoma, 5% gallbladder cancer) had a history of a prior tumor. Median age was 61 years (39-86), 51% were male, and 52% presented with stage IV BTC. The most frequent prior tumors were breast (20%), colorectal (18%), urothelial and prostate (13% each), with a median interval from BTC diagnosis of 9 years (range 0-36). Patients with prior tumors were older (Age>60: 85% vs 70%, p=0.05) and had less stage IV disease (38% vs 55%, p=0.06). FGFR2, IDH1, HER2, and MSI were comparable. Median OS from BTC diagnosis was 25.8 months vs 17.7 months (p=0.59) in patients with and without second tumors, respectively. Among patients with and without a prior tumor, 62.5% and 71% received first-line systemic therapy (32% and 42% chemoimmunotherapy). From the start of first-line therapy, median PFS was 6 months in patients with a prior tumor and 4 months in those without (p=0.51), while median OS was 10 months vs 14 months (p=0.61), respectively.

Conclusion:
A history of prior malignancy is relatively frequent in BTC, most commonly following breast, colorectal, urothelial, or prostate cancers. These patients are typically older and present with less advanced disease. Despite being less likely to receive systemic therapy, their clinical outcomes are comparable to those without prior malignancy, indicating that previous cancer history should not modify clinical management.

PO7-6-YI
HBsAg seroclearance in chronic hepatitis B is protective against hepatocellular carcinoma and decompensation

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Background and aims:
To evaluate HBsAg seroclearance rates in chronic hepatitis B (CHB) patients with and without antiviral treatment, decompensation, and hepatocellular carcinoma (HCC) development rates.

Method:
We retrospectively analyzed CHB patients who followed up at least 1 year and had received or not received antiviral treatment at the gastroenterohepatology outpatient clinic of a tertiary university hospital between 2000-2023. Factors affecting HBsAg negativity and HBsAg loss were investigated. HCC and decompensations developing 1 year after seroclearance were recorded.

Results:
A total of 853 patients in the study [516 (60.5%) male, baseline mean age 37.8 ± 15 years, mean follow-up duration 127.1 ± 77.9 (12 - 288) months] were investigated. Of these, 651 (75.9%) received antiviral treatment, and 202 (24.1%) didn't receive treatment.
62 (7.3%) patients [37 (5.7%) in the treated, and 25 (12.4%) in the untreated group] became HBsAg negative. In the untreated group, 9.1% were HBeAg-positive, and the rest were HBeAg-negative HBV infection. At the last follow-up, all patients in the untreated group were HBeAg negative. In the treated group, 31.3% were HBeAg-positive, and the rest were HBeAg-negative CHB. At the last follow-up, HBeAg loss occurred in 70.7% of treated patients. The time to HBeAg and HBsAg negativity was shorter in those receiving antiviral treatment ($p = 0.002$, $p < 0.001$). HBsAg negativity is higher in those not receiving antiviral treatment ($p = 0.001$). Patients with HBsAg seroclearance had higher baseline AST, ALT, ALP, GGT, and bilirubin levels ($p < 0.05$), and shorter disease duration ($p = 0.003$). There were no differences between the groups in terms of gender, age, HBeAg status, or cirrhotic condition. HBsAg negativity was more frequently in patients with a history of IFN in the treated group ($p < 0.001$). HCC developed in 37 (4.3%), and decompensation in 46 (5.4%) patients, and all of these complications developed in the treated group. HCC and decompensation were higher in cirrhotic patients ($p < 0.001$, $p = 0.006$). None of the patients in the untreated group was cirrhotic at the last follow-up. Patients who developed HBsAg seroclearance were followed for a mean of 42.7 ± 42.6 (12 - 204) months, and no patient developed HCC or decompensation after HBsAg seroclearance.

Conclusion:
HBsAg seroclearance is very rare in the course of CHB, and in our study group, HCC or decompensation didn't develop in any patient who achieved clearance. Cirrhosis was the most important risk factor for HCC.

PO7-7
Performance of the GALAD score in hepatocellular carcinoma surveillance: a systematic review

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Background and aims:
Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers and is the third leading cause of cancer-related mortality worldwide, especially due to late diagnosis. Early detection through surveillance enables curative treatment, but current imaging-based and biomarker approaches remain suboptimal for early HCC detection. In this context, the GALAD score, which combines age, sex, and three serum biomarkers (AFP, AFP-L3%, and DCP/PIVKA-II), has shown promising results for early detection. This systematic review aims to evaluate the diagnostic performance of the GALAD score within the surveillance context.

Method:
A systematic review was conducted to assess the most recent evidence on GALAD-based models for HCC surveillance. Searches were updated to October 8, 2025, in PubMed, Embase, Cochrane Library, and ClinicalTrials.gov. Eligible observational and biomarker validation studies included adults at increased risk for HCC and compared GALAD with conventional surveillance strategies or biomarkers. Studies were excluded if they enrolled patients with previously diagnosed HCC or were outside a surveillance setting. Data extraction was independently performed and cross-checked for accuracy. The protocol was registered in PROSPERO (CRD420251171040).

Results:
A total of 14 studies, including 7.673 participants, were analyzed, mostly observational cohorts or biomarker validation studies. During follow-up (6 months to 6 years), 317 developed HCC. The most common etiology was hepatitis B or C. Mean age ranged from 52 to 63.6 years, mostly males. Most studies compared the GALAD score with biomarkers and confirmed diagnosis with standard-of-care surveillance. Across studies, GALAD consistently showed higher performance. One study reported a sensitivity of 65% (95%CI: 50%-78%) for GALAD versus 35% (95%CI: 22%-49%) for AFP within 6 months of prior diagnosis. Another study found a sensitivity of 72.2% (95% CI 50.0-91.7%) vs 66.7% (95%CI 41.2-88.9%) for AFP for early stage HCC. Additionally, GALAD values in a study could have triggered earlier imaging in advanced cases, reinforcing its role in timely detection.

Conclusion:
The GALAD score showed superior sensitivity for early HCC detection compared to other surveillance methods. Its integration may enhance early diagnosis. However, more data regarding the score is essential for broadening the use of GALAD across different populations.

PO7-8-YI
Gender disparities in hepatocellular carcinoma: implications for screening and treatment allocation

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Background and aims:
Although sex differences in hepatocellular carcinoma (HCC) incidence are well documented, the metabolic profile and treatment allocation among women with HCC remain underexplored.
Current screening strategies may under-recognizing women as an at-risk population. We aimed to characterize sex-specific features of HCC in a real-life cohort and to identify factors influencing treatment eligibility.

Method:
We enrolled 176 HCC patients referred to our Metabolic Liver Disease outpatient clinic. Treatment allocation according to BCLC system, following consultation with a multidisciplinary team of experts. Clinical, metabolic, and radiological variables were compared between males and female, and multivariate logistic regression was used to identify independent associations with female gender.

Results:
Mean age was 69 ys, 79% male. Mean BMI was 27±4.8 kg/m2, with 23% obese, 40% overweight, and 38% diabetic. The main etiologies of liver disease were viral in 62%, alcohol-related in 13%, metabolic in 25%. At diagnosis, 34% had multifocal disease; 12% underwent surgical resection, 77% locoregional therapy, 3% systemic therapy, 8% best supportive care (BSC). 16% developed HCC on a non-cirrhotic liver. Women, compared to men, were older (75±12 ys vs 67±10 ys, p=0.001), less frequently diabetic (23% vs 43%, p=0.04) and overweight (21% vs 47%, p=0.03), with a non-significant trend toward higher obesity (29% vs 21%, p=0.07). Monofocal HCC was more prevalent in women (82% vs 61%, p=0.022). No sex differences were observed regarding etiologies (p=0.4), cirrhosis (p=0.6), or lesion diameter (p=0.49). Despite more frequent monofocal tumors, women were more often allocated to BSC (17% vs 4%, p=0.001). At multivariate analysis, female sex remained independently associated with older age (OR 1.1, 95% CI 1.02-1.13, p=0.02), monofocal HCC (OR 13.3, 95% CI 3.15-25.4, p=0.002), and lower prevalence of overweight (OR 0.27, 95% CI 0.06-0.91, p=0.04).

Conclusion:
Women with HCC were older at diagnosis, showed a lower prevalence of diabetes and overweight but a trend toward higher obesity, and more frequently presented with monofocal tumors.
However, women were less often eligible for active treatment, mainly due to advanced age. These findings highlight the need to consider women, particularly those with obesity, as a high-risk group for HCC. Enhanced surveillance strategies in women may enable earlier detection and improve access to curative therapies.

PO7-9-YI
How liver function defines real-world outcomes with Atezolizumab–Bevacizumab in uHCC

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Background and aims:
Atezolizumab plus bevacizumab is the standard first-line therapy for unresectable hepatocellular carcinoma (uHCC), but data in patients not meeting IMbrave150 eligibility criteria (IMbrave-out) remain limited.

Method:
An French-Italian cohort of 247 patients with unresectable hepatocellular carcinoma uHCC treated with atezolizumab–bevacizumab between 2020 and 2024 was analyzed, comparing outcomes between IMbrave-in and IMbrave-out groups and across five exclusion subgroups: liver impairment, baseline decompensation, adverse clinical conditions, large varices/severe thrombocytopenia, and anticoagulant or dual antiplatelet therapy.

Results:
The median overall survival (OS) was 21.3 months and the median time to progression (TTP) was 9.8 months. The cumulative incidence of hepatic decompensation reached 20%, 30%, and 45% at 6, 12, and 30 months, respectively. IMbrave-out patients (n=176) had significantly shorter OS (13.2 vs 23.8 months, p=0.007) and TTP (p=0.034) compared with IMbrave-in (n=71). Among subgroups, liver impairment was the strongest determinant of poor outcome (median OS 9.5 vs 20.4 months, p<0.001; TTP p=0.032), followed by baseline portal hypertension/decompensation (OS p=0.054). Other exclusion factors, including adverse clinical conditions, varices/thrombocytopenia, or anticoagulant therapy, had limited impact on survival or disease control. Decompensation occurred in 97 patients (≈40% at 30 months), mainly in those with liver dysfunction or portal hypertension. No significant differences in ORR were observed across subgroups. Multivariate analysis identified Child–Pugh B status and ascites as independent predictors of both hepatic decompensation and reduced overall survival, while achieving an objective response was associated with improved outcomes. The occurrence of serious adverse events (SAEs) was independently associated with shorter time to progression.

Conclusion:
Atezolizumab–bevacizumab retains meaningful efficacy and manageable safety in real-world uHCC. Liver dysfunction and portal hypertension remain the dominant drivers of early progression, hepatic decompensation, and reduced survival, whereas other IMbrave150 exclusion factors have minimal impact. Careful liver function assessment is crucial to optimize patient selection and outcomes.

PO7-17-YI
Lenvatinib versus sorafenib as second-line therapy following failure of atezolizumab–bevacizumab in hepatocellular carcinoma: An updated systematic review and meta-analysis.

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Background and aims:
Hepatocellular carcinoma (HCC) is a major cause of cancer-related death worldwide, and while atezolizumab–bevacizumab is established as an effective first-line therapy in unresectable cases, many patients ultimately experience progression and require second-line systemic treatment. The aim of this systematic review and meta-analysis was to compare the efficacy and safety of lenvatinib versus sorafenib as second-line therapies for HCC after failure on atezolizumab–bevacizumab.

Method:
A comprehensive search of four databases (PubMed, Web of Science, Scopus, and Cochrane) was performed according to predefined PICO criteria, targeting patients with HCC who progressed on first-line atezolizumab–bevacizumab. Eligible studies included those reporting clinical efficacy and safety outcomes for lenvatinib and sorafenib up to September 2025.

Results:
Out of 2465 screened articles, 7 studies met inclusion criteria, comprising 542 patients treated with either lenvatinib or sorafenib as a second-line option. Within this pooled cohort, the overall survival at 20 months favored lenvatinib, demonstrating a statistically significant improvement compared to sorafenib, with a risk ratio of 1.41 (95% CI 1.1–1.81, $p < 0.05$) at that time point. Progression-free survival at 6 months also favored lenvatinib, with a risk ratio of 2.21 (95% CI 1.2–4.09, $p < 0.05$). Regarding adverse events, hand-foot skin reaction (any grade) was significantly less frequent in the lenvatinib group (risk ratio 0.56, 95% CI 0.36–0.87, $p < 0.05$). Fatigue rates showed no statistically significant difference between the treatment groups (risk ratio 1.61, 95% CI 0.84–3.1), and a high degree of heterogeneity was detected. Similarly, hypertension rates did not differ significantly between cohorts (risk ratio 1.47, 95% CI 0.97–2.23).

Conclusion:
These findings demonstrate that the observed superiority of lenvatinib over sorafenib as second-line therapy after atezolizumab–bevacizumab failure in hepatocellular carcinoma should be interpreted with caution. Most included studies are observational and subject to potential bias and confounding; thus, the results do not definitively establish the overall advantage of one drug over the other. Further randomized controlled trials are needed to confirm these efficacy and safety differences in a more robust, prospective setting.

PO8-1-YI
Trends in historic aMAP scores in two Hepatocellular carcinoma (HCC) patient groups diagnosed within and outside an HCC surveillance ultrasound scan (USS) programme

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Background and aims:
The aMAP score (based on patient age, gender, albumin-bilirubin levels, platelet count) can quantify HCC risk in patients with chronic liver disease. aMAP is categorised into low-risk (<50), medium-risk (50-59.9) and high-risk (>60) scores. In this study we evaluated aMAP in two groups of HCC patients, one diagnosed as part of routine ultrasound (USS) surveillance and another not diagnosed through the same.

Method:
We studied a cohort of 225 patients (145 cirrhotic and 80 non-cirrhotic) with HCC, of whom169 (~75%) patients were diagnosed outside HCC surveillance USS (Group N, N=No) and remaining 56 (~25%) patients were diagnosed through surveillance USS (Group Y, Y=Yes). We calculated historic aMAP scores in all those patients where blood results were available at 1-year and 5-years before HCC diagnosis.

Results:
At 1-year pre-HCC diagnosis, mean aMAP in group Y (50 patients) of 67.2 was higher than mean aMAP of 65.2 in N (95 patients), [difference not statistically significant (p=0.09 at 95% CI, two-tailed independent t-test)]. At 5-years pre-HCC the means were 64.2 and 62.5 for groups Y and N with the difference again not statistically significant (p=0.24). Within Y group, cirrhotic patients had higher mean aMAP than non-cirrhotic ones at both 1-year and 5-year pre-HCC, (67.1 and 66.7 respectively at 1-year and 64.1 and 63 at 5-years, difference non-significant in both). Interestingly, at 1-year, mean aMAP (67.16) in 50 cirrhotic patients of Y group exceeded that in the 46 non-cirrhotic patients of N group (63.57) at highly statistically significant levels (p=0.007) though the same difference at 5-years was not significant (64.2 vs 61.9, p=0.2). Cirrhotic patients of N group (n= 49) at 1-year had significantly higher mean aMAP (66.7) than non-cirrhotic N patients (63.5) (n= 46) [p=0.018], though the same difference was not significant at 5-years (62.9 vs 61.9, p= 0.5). There were no non-cirrhotic patients in group Y at both time-points.

Conclusion:
Mean aMAP scores in all groups at all time-points were high-risk scores with patients under HCC surveillance having somewhat higher scores. Cirrhotic patients had higher mean aMAP than non-cirrhotic patients though even the latter had a high-risk mean score (>60) at both 1-year and 5-years pre-HCC. We would suggest further work to evaluate the role of HCC risk-scores as screening tools to determine need for surveillance USS in non-cirrhotic chronic hepatitis.

PO8-3-YI
Identifying malnutrition and sarcopenia in patients with hepatocellular carcinoma – a tertiary liver centre experience

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Background and aims:
Hepatocellular carcinoma (HCC) is one of the commonest cancers in incidence and mortality worldwide. Malnutrition and sarcopenia are frequently underdiagnosed in both cirrhosis and cancer patients and associated with poorer outcomes. These dual pathological processes in HCC are likely to exacerbate the rates of malnutrition and sarcopenia, but currently understudied. We aimed to assess the rates of malnutrition and sarcopenia in our HCC patient cohort and observe potential nutrition-related parameters which may associate with worsening clinical status.

Method:
Retrospective audit of patients who underwent a dietetic review within in a specialist HCC clinic at a UK tertiary liver centre in January, May and June 2025. Data was collected from the Trust's electronic patient record including liver disease aetiology, severity, anthropometric measurements (hand grip strength (HGS) and mid-arm muscle circumference (MAMC)), oral nutritional supplementation and documented global nutritional status based on completed dietetic assessment.

Results:
65 patients with HCC underwent a dietetic review. Of these, 81.5% of patients were male and mean age was 65±10 years (range 42-85 years). Cirrhosis was present in 91% of patients – 31% ARLD, 20% MASLD, 15% MetALD and 15% Hepatitis C. Reported global nutritional status deemed 51 (78%) patients to be 'nutritionally deplete'. 78% of compensated (n=41) and 77% of decompensated liver disease (n=22) were deemed 'nutritionally deplete'. Sarcopenia defined by EWGSOP2 demonstrated sarcopenia in 38% of male and 33% of female ≥60 years old patients. Compared to age and sex-matched established national cohort data (NAKO), 100% of female patients and 77% of male patients had HGS <25th centile, with 62% of male ≥60 years old patients having a HGS <5th centile. HGS and MAMC was not correlated to Child-Pugh or MELD score and no significant difference between liver disease aetiologies. 4 decompensated patients and 1 compensated HCC patient had clinical deterioration noted during audit period with HGS and MAMC declining in 80% of cases and for further 1 case no change from low baseline observed.

Conclusion:
Malnutrition and sarcopenia are highly prevalent amongst HCC patients and independent of liver disease severity. Proactive screening is required in all HCC patients. Decline in anthropometric measurements may act as a surrogate for clinical deterioration but larger studies are required to understand and optimise nutrition management strategies in this high-risk cohort.

PO8-4-YI
Cellular immunotherapies beyond checkpoint inhibitors in hepatocellular carcinoma: systematic review of chimeric antigen receptor T cell, T cell receptor engineered, and natural killer cell strategies

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Background and aims:
Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality. Despite advances with immune checkpoint inhibitors (ICI), resistance remains common. Cellular immunotherapies, such as chimeric antigen receptor T cells (CAR-T), T cell receptor (TCR) engineered products and natural killer (NK) cell-based strategies have shown success in hematologic cancers and represent a promising approach for solid tumors. This review analyzes their efficacy, safety, and potential in HCC.

Method:
A systematic review of PubMed, Embase, and the Cochrane Library (2010–2025) identified prospective cohorts and mainly phase I-II trials evaluating CAR-T, TCR-T, or NK-based therapies versus placebo or standard care in adults with HCC. Tumor response and survival outcomes were analyzed. Data were independently extracted and verified. PROSPERO: CRD420251167799.

Results:
Seventeen studies (n = 421) were included, with intervention periods of 8 days to 60 weeks and follow-up of 2 months to 15 years. CAR-T (n = 55; 5 studies, anti-GPC3 and anti-CD133) achieved median progression-free survival (PFS) of 4.6 months and overall survival (OS) of 6 to 12 months, mainly in Barcelona Clinic Liver Cancer (BCLC) C, with stable disease (SD) in 29 patients. TCR-T (n = 55; 6 studies, with 5 hepatitis B virus [HBV] specific TCR-T products [n = 34] and 1 alpha-fetoprotein-targeted autologous T-cell receptor-engineered therapy [n = 21]) showed median PFS of 3 to 7.3 months and OS of 10.9 to 33.1 months, with stabilization in HBV-related or post-transplant recurrence. SD occurred in 45% and progressive disease (PD) in 42%, mostly in BCLC-C. NK-Based therapies (n = 34; 5 studies, with autologous NK, invariant NK T [iNKT], and RetroNectin-activated killer [RAK] cells) had median PFS of 6.5 to 15.1 months and OS between 13 to 36 months, mainly in BCLC C-B, with 21% SD and 12% PD. Cytokine-induced killer (CIK) (n = 144; 1 study) showed 80% mortality reduction and median recurrence-free survival (RFS) of 44 months. Common adverse events were fever, fatigue, transaminase elevation, hyperbilirubinemia, thrombocytopenia, anemia and nausea.

Conclusion:
Cellular immunotherapies showed promising survival and disease control in advanced HCC. NK-based strategies achieved the highest PFS and OS, while HBV-specific TCR-T and CIK therapy were encouraging, particularly in HBV-related recurrence. Larger studies are needed to validate these findings and integrate these therapies into existing treatment strategies and clinical guidelines.

PO8-5
Outcomes of barcelona clinic liver cancer 2022 guideline-discordant escalation in hepatocellular carcinoma vary by a simple performance–liver function–tumour diameter phenotype

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Background and aims:
Adherence to Barcelona Clinic Liver Cancer (BCLC) 2022 guideline pathways in hepatocellular carcinoma (HCC) varies widely. We examined whether BCLC 2022 guideline-discordant treatment escalation relates to overall survival (OS) after a 90-day landmark and whether a bedside phenotype combining performance, liver function and tumour diameter modifies this association. The phenotype (EAD) assigns one point for Eastern Cooperative Oncology Group performance status (ECOG) ≥1, albumin–bilirubin (ALBI) grade ≥2 and maximum tumour diameter ≥50 mm; low risk = 0–1, high risk = 2–3.

Method:
Single-centre retrospective cohort study. Of 428 patients screened, 311 met eligibility criteria; after applying a ≥90-day landmark, the primary analysis set included n=279. Guideline adherence was classified as BCLC 2022 guideline-discordant escalation (yes/no). Treatments and baseline characteristics were evaluated using SPSS software. The primary outcome was OS. Cox proportional hazards models were adjusted for ECOG, tumour size, ALBI grade, treatment era ≥2020, and the logit of a propensity score. Effect modification by the EAD phenotype (ECOG–ALBI–Diameter) was tested, followed by stratum-specific Cox models within EAD-low and EAD-high groups.

Results:
Kaplan–Meier analysis after the 90-day landmark after the 90-day landmark showed shorter survival with escalation: median OS 20.7 months (95% confidence interval [CI] 15.9–25.6) vs 40.1 months (27.6–52.6); log-rank p=0.008. In adjusted models the overall association was not significant (hazard ratio [HR] 1.16, 95% CI 0.86–1.58, p=0.34). EAD significantly modified this association (interaction p=0.035). In EAD-low (0–1; n=99), escalation was linked with worse OS (HR 2.06, 95% CI 1.14–3.32, p=0.016). In EAD-high (2–3; n=180), the association was null (HR 1.00, 95% CI 0.68–1.47, p=0.987).

Conclusion:
After addressing immortal-time and confounding by indication, the impact of BCLC 2022 guideline-discordant escalation depends on a simple phenotype—harmful in EAD-low, neutral in EAD-high. This tool may help select patients for (or against) escalation and warrants prospective validation.

PO8-6-YI
Effectiveness of home-based digital exercise interventions on physical function in patients with primary liver cancer: a systematic review and meta-analysis

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Background and aims:
Digital and home-based exercise interventions may improve physical rehabilitation and engagement after treatment for liver cancer. This systematic review and meta-analysis aimed to assess their effects on physical function and exercise adherence.

Method:
A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Cochrane Library for studies published up to June 2025. After screening 569 articles, 3 studies met inclusion criteria. The primary outcomes analyzed were changes in grip strength (kg) and lower limb function measured by the 5-repetition sit-to-stand test (seconds) before and after a digital/home-based exercise intervention.

Results:
Three eligible studies were included. The pooled mean increase in grip strength was 2.74 kg (95% CI: –0.34 to 5.82), and the mean reduction in 5-repetition sit-to-stand time was –1.33 seconds (95% CI: –3.80 to 1.14) following intervention. Heterogeneity was substantial for the sit-to-stand outcome. Exercise adherence was moderate to high: 36% of patients achieved ≥80% of recommended exercise time in one study and the average attendance to planned sessions was 76% in another, indicating good engagement with home-based digital programs

Conclusion:
Home-based digital exercise interventions in liver cancer patients appear to increase engagement and may improve physical function, though the evidence is still limited. Additional high-quality research is needed to confirm clinical benefit and to optimize intervention strategies.

PO8-7-YI
Stereotactic Body Radiotherapy for the treatment of HCC: a single centre experience

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Background and aims:
Stereotactic body radiotherapy (SBRT) is a highly precision radiotherapy techniques that delivers ablative doses (>6–7 Gy) to small target volumes using multiple convergent beams. It represents as alternative treatment for Hepatocellular Carcinoma (HCC) in patients ineligible for surgery or other locoregional therapies. This study aimed to evaluate the efficacy and safety of SRBT in HCC patients treated at Niguarda Hospital (Milan) over a four-year period

Method:
All consecutive patients who underwent SBRT for HCC between June 2021 and July 2025 were included, regardless of tumor size or clinical condition. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan–Meier method, and treatment response was assessed by mRECIST criteria. Local control (LC) included complete response (CR), partial response (PR), and stable disease (SD).

Results:
Forty-nine patients, with a median age of 78 years, were treated during the period study, mostly with a mean dose of 50 Gy. Chronic liver disease was present in 80% of cases, and the median tumor size was 1.8 cm. Median follow-up was 8.2 months (95% CI: 15.1–30.4). At six months, OS, and PFS were 73.2% (95% CI: 61.5–81.8), and 35.8% (95% CI: 25.1–46.7), respectively. Local control was achieved in 42 patients (87.5%; CR 37.5%, PR 18.5%, SD 31.25%). A single case of radiation-induced liver injury (RILI) was recorded in our cohort, requiring reduction in radiation dose. Tumor volume ($p = 0.02$) and dose ($p = 0.041$) correlated with treatment response, while progression pattern (systemic vs intrahepatic) was the only factor associated with survival ($p = 0.01$). For the entire period of follow up, twenty-six patients experienced progression; systemic therapy and best supportive care were offered respectively to 26.9% and 34.6%.

Conclusion:
SBRT is an effective and safe therapeutic option for patients with unresectable or recurrent HCC, providing local control comparable to other locoregional treatments. Further randomized studies are warranted to confirm its role as a standard alternative approach

PO8-9
Predictors of HCC Recurrence Post-Treatment: considerations for future post treatment imaging surveillance

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Background and aims:
(HCC) has a high recurrence rate even after potentially curative therapy, around 70% of patients have recurrence within 5 years. There is no agreed protocol on post treatment surveillance and protocols vary across centres. Prior studies suggest tumor size, nodule number, alpha-fetoprotein (AFP) , and patient factors may influence recurrence.The recently developed aMAP score (age, male sex, albumin, bilirubin, platelets) predicts 5-year HCC risk in the pre-cancer setting, but its utility for recurrence prediction is not fully determined.
To determine clinical and tumor-related predictors of HCC recurrence after initial treatment including patient, biochemical, tumour and existing treatment risk prediction models. e.g. Duvoux/AFP model), aMAP risk score to see if future models could be used to predict HCC recurrence to develop new treatment strategies and monitoring.

Method:
A retrospective analysis of 654 HCC patients (median 67 years, 76% male). Recurrence outcomes were assessed in 324 patients who had received treatment for BCLC 0-B disease. Data collected included gender, age, etiology, diabetes, liver stiffness, and biochemical parameters as well as and staging models for HCC. A Comparison of patients with recurrence versus no recurrence was performed.

Results:
HCC recurred in 189/324 treated patients (58%). Recurrence was greater in males (85.6% vs 66.2% of non-recurrence, $p<0.01$). Recurrent HCC had more aggressive disease: 37% multifocal tumors (vs 24) and median largest tumor was 30 mm vs 22 mm. Recurrence assocaited with worse liver disease,(platelet - 137k vs 163), low albumin (<36 g/L,18% vs 10%) and elevated bilirubin (>17 µmol/L 29% vs 19%). The aMAP score was higher in the recurrence group (65 vs 60). There was no significant difference in age or etiology between groups. Diabetes was more prevalent in recurrent disease (43% vs 35%, p=NS).AFP was higher in the recurrence group (8 ng/mL vs 5 ng/mL), and more patients had AFP >100 ng/mL (14% vs 10%). Duvoux score (>2 points, reflecting tumor >6 cm, ≥4 nodules or AFP >1000) were more likely to recur (30% vs 20% of patients with score ≤2). On multivariate analysis, male gender (hazard ratio ≈1.5) and multifocal tumor were independent predictors of recurrence.

Conclusion:
HCC recurrence is associated with male sex and initial tumor burden.Patients with recurrent disease had higher aMAP scores, suggesting aMAP may help identify increased post-treatment recurrence. Risk based strategies are needed.

PO8-10-YI
Prospective assessment of the quality of multidisciplinary team meeting for the management of hepatocellular carcinoma.

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Background and aims:
Multi-disciplinary Team (MDT) brings diverse domain-specialists together in a single forum to optimize individualized patient-centric decision-making. In this study, we aim to prospectively assess a single-center MDT for hepato-cellular carcinoma (HCC).

Method:
HCC patients with LI-RADS 5 (Liver Imaging Reporting and Data System category 5) lesions discussed in weekly MDT meetings between July-September 2024 were prospectively included. Two cases from each MDT meeting were chosen after computer randomization to assess inter assessor variability. Quality of the MDT meeting was assessed using MDT MODe-II and MDT MODe-Lite (Metric for the Observation and Decision Making, *PMID:21610266, 33974197*). MDT-MODe measures quality of presented patient information and disciplinary contribution to patient reviews. MDT-MODe Lite has six domains-clinical input, holistic input, clinical collaboration,pathology, radiology and management score.

Results:
Sixteen MDT virtual sessions were analyzed. Six, 5-13; (median ,range) patients' details with HCC were discussed over 66.5 (58-84) minutes in a single session. Individual domain experts were present during these meetings.Of the 299 patients discussed in these meetings,122 (41%) patients had HCC {Age: 59, 22-77 years; M: 86%; common etiology-Metabolic: 33.6%, Hepatitis B: 36%; MELD-10 (6-46); past treated HCC 44 (36%). All patients had cross-sectional imaging discussed by radiologists, multifocal – 33 (27%), tumor in vein- 39 (31.9%) and metastasis 12 (9.8%). Only a minority (2, 0.1%) had available histology for discussion. The final diagnosis, treatment and follow up plan were well-documented for all patients.

Global score using MDT MODe-II was 41 (41- 49, maximum-65), MDT-MODe-Lite was 14 (12-16, maximum-18). Both the scores were equal in performance to assess MDT (r: 0.821; p-value: <0.05). Inter-assessor agreement on both scores using kappa coefficients {kappa:0.925 (MODe Lite) and 0.752 (MDT MODe-II)} showed good reliability across all domains and global scores.

Conclusion:
Both scores MDT MODe-II and MDT-MODe Lite performed equally towards assessing performance of MDT in HCC. Given the limited role of histology of many HCCs, a tailored score needs to be designed for assessment and effectiveness of HCC MDT.

PO8-13
The effect of HBV-DNA level changes on tumor recurrence in resected HBV-HCC patients: A multi-center study

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Background and aims:
To investigate the significance of perioperative HBV-DNA changes for predicting recurrence in patients with HBV-related hepatocellular carcinoma (HCC) who underwent liver resection (LR).

Method:
From 2013 to 2020, 241 HBV-related HCC patients who underwent LR in five Hallym university-affiliated hospitals were enrolled. Serum HBV-DNA level was analyzed for association with HCC recurrence, together with other clinicopathological variables.

Results:
Before LR, 99 patients had undetected HBV DNA and 142 had detectable viral level preoperatively. Of the 142 patients with a detectable viral level, 72 rapidly progressed to undetected viral level within 3 months after LR (Rapid group) and 70 showed persistent detection (Non-rapid group). The rapid group had a better recurrence-free survival (RFS) rate than the non-rapid group (1-, 3-year RFS=75.4, 57.3 vs. 54.7, 39.9 %, p=0.012). In subgroup analysis, rapid group had better RFS rate in early stage (1-, 3-year RFS=82.6, 68.5 vs. 62.8, 45.8%, p=0.005), however, the RFS rates between the two groups were comparable in the advanced stage (1-, 3-year RFS=61.1, 16.7 vs. 45.5, 22.7%, p=0.994). Among the 142 patients with preoperatively detected HBV-DNA, rapid progression to HBV undetection within 3 months (Hazard ratio [HR]=1.7, p=0.022), large tumor size (HR=2.7, p<0.001), multiple tumors (HR=3.2, p<0.001), and microvascular invasion (HR=1.7, p=0.028) were independent risk factors for RFS in multivariate analysis.

Conclusion:
Rapid HBV-DNA undetection after LR is associated with better prognosis for recurrence in HCC patients. Therefore, appropriate treatment and/or screening may be necessary for patients who do not return to viral undetection after LR.

PO8-14
Post-transplant survival and causes of death in patients with hepatocellular carcinoma according to standard exception model for end-stage liver disease allocation

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Background and aims:
Liver transplantation (LT) is considered an established treatment for patients with hepatocellular carcinoma (HCC). Although survival continues to improve, post-transplant mortality remains significant. This study presents descriptive results on survival, recurrence and causes of death stratified by standard exception model for end-stage liver disease (SE-MELD) allocation.

Method:
A total of 164 patients who underwent LT for HCC between 2008 and 2022 were analysed. Collected data included patient characteristics, tumour and treatment details, peri-/postoperative course and outcomes. Deaths were classified as recurrence, infections/sepsis, other malignancies, graft failure/rejection, cardiovascular causes, gastrointestinal complications, others or unknown. The retrospective evaluation was descriptive, based on absolute numbers and percentages.

Results:
The cohort comprised 164 patients, 26 % female and 74 % male. Overall survival was 65 % at 5 years and the median follow-up period was 56.5 months. SE-MELD status was assigned to 42 % of patients while 58 % were transplanted without exception status. The most common cause of death was recurrence (25 %) followed bei infections/sepsis (17 %). Graft failure/rejection accounted fore 13 % of deaths, other malignancies and cardiovascular causes each represented 10 %. Gastrointestinal complications contributed to 4 % and 7 % were classified as others. Stratified by SE-MELD, recurrence was also the leading cause of death (30 %) in non SE-MELD patients, whereas cadiovascular causes predominated in SE-MELD patients (21 %), with recurrence at 17 % of deaths. The incidence of deaths due to graft failure/rejection was identical in both groups (13 %). Overall, recurrence occured in 23 % of patients, with 3 % intrahepatic only, 57 % extrahepatic only (predominantly pulmonary, 61 %) and 41 % both intra- and extrahepatic.

Conclusion:
This retrospective study assessed post-transplant outcomes in HCC patients. While recurrence remained the leading cause of death, infections/sepsis represented a considerable contribution to overall mortality, highlighting potential for improvement. Notably, deaths from graft failure/rejection were similar across SE-MELD and non-SE-MELD patients, suggesting comparable organ quality regardless of allocation.

PO8-15-YI
Real-world outcomes of first-line Durvalumab plus gemcitabine-cisplatin in advanced biliary tract cancers : results from a French retrospective monocentric cohort

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Background and aims:
Durvalumab plus gemcitabine-cisplatin is now the first-line therapy for advanced cholangiocarcinoma (CCA) and gallbladder cancer (GBC) according to the TOPAZ-1 trial. Real-world data remain limited. This study evaluated treatment efficacy, safety and prognostic factors associated with response and survival.

Method:
We retrospectively included patients who received ≥ 1 cycle of durvalumab plus gemcitabine-cisplatin for advanced or metastatic CCA or GBC between August 2022 and September 2025 at Paul Brousse Hospital (Villejuif, France). Clinical, biological, radiological, histological and molecular data, treatment details, adverse events and outcomes were collected. Overall survival (OS), progression-free survival (PFS), prognostic factors and safety were analyzed, using Python (v3.12).

Results:
80 patients were included (median follow-up 10.5 months); median age was 65 years and 49% were male. Cirrhosis was present in 7.5%, 50% had ECOG ≥ 1. 54% had intrahepatic CCA, 26% perihilar CCA, 20% GBC. 37% relapsed after prior surgery (median time to relapse 10.5 months). 64% were metastatic and median CA19.9 level was 167 kUI/L. Molecular profiling was available for 62 patients (77%); 26 (42%) with actionable alterations.

Median OS and PFS were 18 and 8 months. In multivariate analysis, metastatic disease was associated with shorter OS (HR 4.49, 95% CI 1.05-19.1, p = 0.04) and PFS (HR 3.03, 95% CI 1.36-6.76, p = 0.006). Recurrence after surgery was associated with longer OS (HR 0.33, 95% CI 0.11-0.97, p = 0.04). Lymph node involvement was associated with shorter PFS (HR 2.2, 95% CI 1.13-4.27, p = 0.02). At first assessment (3 months), the objective response rate was 20%. Actionable alterations were associated with better response (Chi-square, p = 0.03), and GBC localization with poorer response (Chi square, p = 0.04).

Patients received a median 8 cycles of treatment. Dose reductions occurred in 60%, grade ≥ 3 hematologic toxicity in 32%, and immune-related adverse events in 14%, with 5 severe cases causing durvalumab discontinuation.

At data cut-off, 36 patients (45%) had progressive disease: 28 (78%) received second-line therapy (FOLFOX 78%, FOLFIRI 11%, targeted therapy 11%).

Conclusion:
In this real-world cohort, durvalumab plus gemcitabine-cisplatin showed efficacy and manageable toxicity. Median OS exceeded that in TOPAZ-1, suggesting more favorable outcomes. Metastatic disease and nodal involvement were adverse factors, while recurrence after prior surgery was associated with better survival.

PO8-16
Intermediate-stage hepatocellular carcinoma is an ideal candidate for TACE combined with targeted and immunotherapy: A systematic review and meta-analysis based on randomized controlled trials

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Background and aims:
In recent years, several large-scale, multicenter, randomized controlled trials (RCTs) have evaluated the efficacy of transarterial chemoembolisation (TACE) combined with targeted therapy and immunotherapy compared to TACE alone. However, based on Barcelona Clinic Liver Cancer (BCLC) staging, although approximately 50% to 60% of patients across these studies were classified as BCLC stage B, up to 40% were categorized as either stage A or C. Therefore, the optimal patient subgroup that would derive the greatest benefit from combination therapy remains to be clearly defined.

Method:
A systematic review and meta-analysis were conducted based on data reported from three RCTs (EMERD-1, LEAP012, and TALENTACE) that evaluated the efficacy of transcatheter arterial chemoembolization (TACE) in combination with targeted therapy and immunotherapy compared to TACE alone. A total of 1231 patients were included across the studies. The primary endpoint was the comparison of PFS, while the secondary endpoints were the ORR and treatment-related adverse events (TRAEs).

Results:
For unresectable HCC, the median PFS associated with TACE in combination with targeted therapy and immunotherapy ranged from 10.3 to 15.0 months, which was significantly longer than that achieved with TACE alone (6.3-10.0 months). A meta-analysis of data from three RCTS showed that median PFS was significantly improved in the combination group compared with TACE alone (HR: 0.69, 95% CI: 0.60-0.80). The results of post hoc analysis using subgroup data from the EMERALD-1 and LEAP-012 trials showed that the combination therapy significantly improved the median PFS of BCLC stage B patients compared with TACE alone (HR: 0.64, 95% CI: 0.51-0.80). However, no statistically significant benefit was observed in patients with BCLC stage A (HR: 0.74, 95% CI: 0.54-1.03) or stage C (HR: 1.02, 95% CI: 0.66-1.55). According to the Response Evaluation Criteria in Solid Tumors version 1.1, the ORR of TACE combined with targeted therapy and immunotherapy was significantly higher compared to TACE alone (OR: 1.73, 95% CI: 1.37-2.18). However, the incidence of TRAEs of grade 3 or higher was also significantly increased (OR: 4.04, 95% CI: 2.18–7.49).

Conclusion:
TACE combined with targeted and immune triple therapy significantly improved mPFS in patients with unresectable HCC. Patients with BCLC stage B HCC may represent the most suitable candidates for triple therapy.

PO8-17
Impact of bridging therapy response on dropout rates in HCC Patients awaiting liver transplantation

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Background and aims:
Hepatocellular carcinoma (HCC) is a leading indication for liver transplantation (LT). Prolonged waiting times can result in patient dropout from the transplant list. Bridging therapies are employed to control tumor progression and prevent dropout. This study aims to evaluate the association between response to bridging therapy and the risk of dropout in HCC patients awaiting LT.

Method:
We conducted a retrospective cohort study of HCC patients listed for LT (2009-2019) at HCFMUSP. Survival probabilities were estimated using the Kaplan-Meier method and compared with the Log-Rank test. The impact of treatment response on dropout was assessed using Cox regression analysis.

Results:
Of 519 patients listed for LT, 320 underwent bridging therapy. TACE was the most common initial bridging therapy (68.3%), followed by RFA (23.6%) and PEI (6%). Among patients that received bridging therapy, 218 patients underwent transplantation, while 102 (31.8%) experienced dropout. The median waiting time on transplant list was longer for patients who experienced dropout compared to those who underwent transplantation (11.5 vs. 7 months). Patients who underwent transplantation had better baseline liver function, as reflected by a higher proportion of Child-Pugh A scores (72.9% vs. 65.3%). A complete response to the initial bridging therapy was less frequently observed in patients who experienced dropout (32.4% vs. 46.3%, p = 0.002). The cumulative probability of dropout was significantly higher in patients exhibiting progressive disease at 6, 8, and 12 months (16.9%, 26.4%, and 40.9%, respectively). Cox regression analysis revealed that patients with progressive disease had a 2.86-fold increased risk of dropout (HR 2.86, 95% CI \[insert CI values here]).

Conclusion:
Response to initial bridging therapy significantly influences dropout rates in HCC patients awaiting liver transplantation. Progressive disease following bridging therapy is associated with longer waiting times on transplant list and leads to a significantly higher risk of dropout.

PO9-1
High LAG-3 and FGL1 expression as prognostic in hepatocellular carcinoma: a systematic review

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Background and aims:
Hepatocellular carcinoma (HCC) is the most common primary liver malignancy worldwide, associated with high mortality and poor overall survival. In HCC, increased expression of LAG-3, a marker of $CD4^+$ and $CD8^+$ T-cell exhaustion from chronic antigenic stimulation, has been observed. This receptor functions as an immune checkpoint, inhibiting T-cell proliferation and cytokine secretion. The recent identification of fibrinogen-like protein 1 (FGL1) as the ligand of LAG-3 has attracted interest for its prognostic relevance. Upon binding to FGL1, LAG-3 is activated and exerts immunosuppressive effects on T cells. This systematic review (SR) aims to evaluate the prognostic significance of LAG-3 and FGL1 overexpression in HCC by comparing tissues exhibiting high and low expression levels of these markers.

Method:
This review followed PRISMA guidelines. PubMed, Cochrane, and Embase databases were searched up to October 2025. Studies were categorized according to biomarker expression, immunoregulatory function, and prognostic or survival outcomes. PROSPERO ID: CRD420251171053.

Results:
Eleven studies involving 2,136 patients were included: 9 retrospective cohorts, 1 case–control study, 1 prospective translational study. Eight studies (n = 1,327) evaluated overall survival (OS). In one study, patients with high LAG-3 expression had a mean OS of 31.85 months, compared to 42 months in those with low LAG-3 expression, suggesting that elevated LAG-3 levels were associated with poorer prognosis. Similarly, high FGL1 expression was also correlated with worse OS ($p < 0.03$). Another study reported that patients with low LAG-3 expression had a progression-free survival (PFS) of 465 days, whereas those with high LAG-3 expression had a PFS of only 88 days. FGL1-positive tumors showed higher rates of progression (65.2%) and metastatic potential ($p = 0.020$). Additionally, six studies (n = 381) demonstrated a significant association between high LAG-3 expression and advanced TNM (tumor, nodes and metastasis) stage ($p < 0.001$), as well as increased metastasis.

Conclusion:
High expression of LAG-3 and FGL1 is associated with tumor progression, increased metastatic potential, and consequently poor prognosis and advanced disease in untreated HCC, reflecting a state of T-cell exhaustion. These findings support LAG-3 and FGL1 as potential prognostic biomarkers in HCC. Further prospective multicenter studies are warranted to confirm their predictive value and validate their clinical utility in oncology.

PO9-2
Use of Stereotactic Ablative Radiotherapy as a Locoregional Treatment Option for Hepatocellular Carcinoma – Outcomes at a Regional Centre

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Background and aims:
Stereotactic ablative radiotherapy (SABR) is high-precision, high-dose radiation treatment. In recent years SABR has emerged as an effective non-invasive management option for early-stage hepatocellular carcinoma (HCC) in cases unsuitable for or refractory to other locoregional treatments. The aim of this project was to evaluate initial outcomes for patients treated with SABR for HCC at our regional referral centre.

Method:
We retrospectively analysed patients with HCC treated with SABR over a 26-month period (02/2023-05/2025). Treatment regimens included 40-50 Gy in 3-5 fractions. The primary outcome was local control rate (LCR) assessed via cross-sectional imaging and multidisciplinary team (MDT) consensus. 12-month survival estimates were based on Kaplan-Meier methods. Univariate Cox regression analysis was used to compare estimated survival data by tumour size, biologically effective dose (BED), Child-Pugh (CP) score, and ALBI score.

Results:
We identified 64 tumours treated in 56 patients. Median follow-up was 10.6 months (range 0.7- 28.2). Median age was 60 (range 35-90). All were CP A (A5 86%, A6 14%) or ALBI 1-2 (1: 66%, 2: 34%) and performance status 0-2 (0: 20%, 1: 64%, 2: 16%) at baseline. SABR was used first line in 19 patients (34%). Reasons for opting for SABR included: failure of previous treatments (38%), co-morbidities (30%), tumour size/position (25%), and patient preference (7%). Eight (14%) were treated with intention to bridge to liver transplant. Three of these had transplants at the time of analysis.

Estimated 12-month LCR was 88.8% (95% CI 75%, 95%), with 5 patients (9%) showing recurrence within the high-dose treatment area. Three patients (5%) had a CP score increase of ≥2 post-treatment. No patients died within 30 days post-SABR.

Estimated 12-month progression-free survival (PFS) was 69.4% (95% CI 52%, 81%). Estimated 12-month overall survival (OS) was 73.6% (95% CI 57%, 85%). No statistically significant differences in LCR, PFS or OS were found between BED, CP, and ALBI score groups. However, for patients with smaller tumours (<3cm) there was a trend for improved OS (p=0.06).

Conclusion:
Our centre's LCR aligns with current literature, supporting SABR as a safe and effective locoregional treatment for HCC. Larger cohorts and longer follow-up are needed to identify key prognostic factors and refine patient selection. Further studies will help clarify SABR's role alongside other locoregional and systemic therapies.

PO9-3-YI
Modelling of Patient-Specific Liver Vasculature and Sorafenib Pharmacokinetics in Hepatocellular Carcinoma

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Background and aims:
Liver cancer is the second leading cause of cancer-related deaths. Despite the various therapeutic options for hepatocellular carcinoma (HCC) treatment, selecting patient-specific therapy remains challenging. A major challenge is predicting the distribution and heterogeneity of anti-cancer medication in the liver due to factors such as liver anatomy, vascular topology, perfusion, tumour location. In this study, we applied a recently published algorithm (Jessen E, et al. 2022) to generate vessel trees within a defined liver volume and modelled the spatio-temporal pharmacokinetics of the multi-kinase inhibitor sorafenib (NEXAVAR®) within the liver. Our objectives were: (i) to generate physiologically realistic arterial, portal, venous, and biliary trees in a given liver volume; (ii) to develop a mechanistic pharmacokinetic model for substance transport in these trees; (iii) to couple this model with a physiologically based pharmacokinetic (PBPK) model of sorafenib; (iv) to simulate drug concentration dynamics within the liver.

Method:
Substance transport along the vessel and biliary trees was modelled using ordinary differential equations. Each terminal segment of the trees was associated with a terminal liver volume, representing the hepatic tissue supplied by individual terminal arterial, portal, venous, and biliary segments. In each terminal volume, the local sorafenib metabolism and biliary excretion were modelled. Model performance was evaluated using published pharmacokinetic data.

Results:
The algorithm successfully generated physiologically realistic arterial, portal, venous, biliary trees within the liver volume. The surrogate mechanistic–PBPK model reproduced published pharmacokinetic data for sorafenib and enabled spatially resolved predictions of drug concentrations along the vascular and biliary trees and within liver tissue. Simulations revealed that the time to reach maximum sorafenib concentration in liver tissue was directly related to proximity to the start of inflow trees and inversely to proximity to the end of outflow trees. These results underscore the influence of the liver anatomy, its vascularisation topology and target location on intrahepatic drug exposure, suggesting that individualised dosing strategies could enhance therapeutic response in HCC.

Conclusion:
The established workflow for simulating the spatial distribution and heterogeneity of anti-cancer medication in a given liver anatomy can provide important information for individual HCC treatment planning.

PO9-4-YI

Safety and efficacy of Lenvatinib in elderly patients with hepatocellular carcinoma: a systematic review and meta-analysis

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Background and aims:
Hepatocellular carcinoma (HCC) is increasingly diagnosed in older adults, and aging populations present unique challenges in cancer management due to potential differences in drug tolerability and treatment efficacy. This study aims to systematically assess and compare the safety and efficacy of lenvatinib in elderly (≥75 years) versus non-elderly patients with hepatocellular carcinoma.

Method:
A comprehensive literature search was conducted across PubMed, Cochrane Library, Scopus, and Web of Science databases up to September 2025. Studies were eligible for inclusion if they were randomized controlled trials or observational studies evaluating lenvatinib in elderly HCC patients vs non elfderly,with elderly age defined as 75 years or older. Data were extracted on efficacy outcomes such as overall survival, progression-free survival, and objective response rate, and safety outcomes reported in adverse events. Pooled effect estimates were calculated using appropriate statistical models based on outcome type.

Results:
Of the 1842 articles initially screened, 8 studies were ultimately included. The meta-analysis found no significant difference in overall survival between elderly and non-elderly patients treated with lenvatinib, with a pooled hazard ratio of 1.02 (95% CI: 0.84–1.24), and no evidence of heterogeneity. Similarly, progression-free survival did not differ statistically between cohorts, as reflected by a hazard ratio of 1.08 (95% CI: 0.93–1.26). The objective response rate was also comparable, with a risk ratio of 0.98 (95% CI: 0.83–1.15). In terms of adverse events, elderly patients had a significantly lower risk of experiencing hand-foot skin reaction (risk ratio 0.52; 95% CI: 0.31–0.9; $p < 0.05$), while the incidence of decreased appetite (risk ratio 1.7; 95% CI: 0.75–3.85) and hypertension (risk ratio 1.2; 95% CI: 0.63–2.29) was similar between groups.

Conclusion:
This study suggests that lenvatinib may provide similar efficacy and safety for elderly patients with hepatocellular carcinoma as for younger patients. However, given potential limitations such as quality and design of the included studies, more rigorous, adequately powered randomized studies are needed to confirm these observations and better guide clinical decision-making regarding the use of lenvatinib in elderly populations.

POSTER ABSTRACT PRESENTATIONS

Nurses & AHPs

PO4-5-YI
Pilot study to explore the lived experience of Black patients diagnosed with Advanced Hepatocellular Carcinoma in a tertiary hepatocellular (HCC) centre in the United Kingdom (UK)

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Background and aims:
In the UK, Black patients with HCC face disproportionate barriers to equitable healthcare. Due to higher rates of undiagnosed hepatitis B, co-existent socioeconomic deprivation, unequal access to surveillance and specialist treatment. Structural factors contribute to later presentations, poorer outcomes. It is recognised that Black patients are underrepresented in patient experience and clinical trials. Addressing such variations is essential to ensure fair delivery of care. This project aimed to understand service and structural biases in healthcare for Black patients with HCC and explore their lived experience.

Method:
Single, regional centre, unmet need identified for Black patients following analysis of non-attendance to clinic, time to treatment, index presentation and support needs. Over 6 months, focused interviews conducted. Inclusion - self-reported Black African and/or Black British adults, diagnosed advanced HCC, planned or commenced anti-cancer therapy. Clinical nurse specialist conducted interviews using National Cancer experience survey as basis. Subsequent long form questions incl. adjustment to diagnosis, social support, engagement and opinions about support from care team. Data was analysed using mixed methods.

Results:
Individual interviews conducted with 8 patients to understand lived experience of cancer and support. Patients were male with a median age 51.5 years (22-78). Consistent concerns - financial wellbeing, access to support and the cost of cancer. In particular, patients report insecurity for housing, risk of unemployment, lack of sick pay and need to attend multiple appointments. 3 patients were socially isolated or had very little support. Experience of medical care was rated highly including access to dedicated specialist nurses. Some patients had strong social networks through community & religious groups, these were often the main source for holistic support for social and emotional well-being. Stigma was also highlighted. Distress scored highly.

Conclusion:
Despite small cohort, there seems to be urgent need to increase support for Black patients with HCC. This includes navigating financial challenges associated with multiple hospital appointments, unemployment, benefits and housing concerns. It is also important to understand the role other social networks can play in holistic management including peer support, engagement with wider communities. Further service review underway to understand the impact of social deprivation for patients with HCC.

POSTER ABSTRACT PRESENTATIONS

Public Health

PO1-05
The burden of MASH-related liver cancer in Canada in 2021 and its trends from 1990 to 2021 in comparison to global estimates

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Background and aims:
Metabolic dysfunction-associated steatohepatitis (MASH) affects over 5% of Canadians and is a leading cause of liver-related morbidity and mortality. The annual progression rate to liver cancer (hepatocellular carcinoma (HCC)) among patients with MASH is reaching 2% per year. Our study aimed to assess the burden of MASH-related liver cancer in Canada in 2021 and its trends from 1990 to 2021.

Method:
Data on liver cancer due to MASH were retrieved from the Global Burden of Disease (GBD) 2021 Study results (source: Institute for Health Metrics and Evaluation, used with permission). We evaluated incidence, prevalence, Disability-Adjusted Life Years (DALY), and mortality in Canada and compared them to the global estimates. Data were presented as age-standardized rates with 95% uncertainty intervals (95%UI). The percentage changes between 1990 and 2021 were calculated.

Results:
The incidence of MASH-related liver cancer in Canada increased 2.73 times, from 0.26 [95%UI 0.19-0.35] per 100,000 population in 1990 to 0.71 [0.51-0.97] in 2021, while the global incidence increased by 36% (from 0.36 [0.29-0.45] to 0.49 [0.40-0.60]). The prevalence in Canada increased 3.16 times (1.01 [0.74-1.36] vs. 0.32 [0.23-0.42]), while worldwide the increase was 53%. During 1990-2021, the DALY rate in Canada increased 2.43 times compared to a 19% increase globally. There was a 3-fold increase in the mortality rate in Canada (from 0.22 [0.16-0.30] to 0.66 [0.47-0.91]) vs. a 23% global increase.

Conclusion:
Tripling the rates of MASH-related liver cancer in Canada over the last three decades poses a substantial public health risk. It requires the development and wide implementation of effective preventive, screening and management strategies.

PO1-07-YI

Sex differences in liver cancer mortality trends in the US: role of cancer type, etiology, and birth cohort

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Background and aims:
Primary liver cancer is the third leading cause of cancer deaths worldwide and has some of the worst 5-year survival rates. Sex differences in liver cancer mortality have been long recognized, with men generally showing higher rates. These disparities come from hormonal influences and different exposures to risk factors like HCV and alcohol, although in recent years, rising metabolic risk factors have shifted these patterns. The role of these factors in sex-based disparities remains unclear. This study aims to analyze recent trends in liver cancer mortality across the U.S. population, focusing on how cancer subtypes (HCC vs. iCCA) and generational differences influence sex-based disparities.

Method:
The CDC WONDER Online Database was used to study primary liver cancer cases from 1999-2020 and 2018-2023. The incidence and mortality rates were calculated based on gender, age, race, and stage of diagnosis. Joinpoint regression software was used separately by sex and cancer type on log-transformed age-standardized death rates. From the analytic mortality files, rates were calculated separately for HCC and iCCA in males and females for each year at death and age at death; Constrained Generalized Linear Models were employed to address the identification problem.

Results:
534,526 liver cancer deaths were recorded in the U.S. from 1999 to 2023. HCC mortality increased until 2012-2013, then plateaued for several years before beginning to decline. In males, mortality started to decrease from 2017 (Annual percent change—APC =−0.9, $p < 0.05$), while in females, mortality continuously increased over time. In contrast, mortality from iCCA increased in both males (APC 1999-2023= 3.2, $p<0.05$) and females (APC 1999-2023= 3.6, $p<0.05$).

Conclusion:
While mortality among males has decreased in recent years due to the impact of HCV treatment, female mortality continues to rise, mainly driven by HCC related to MASLD and iCCA. These findings highlight the ongoing epidemiological shift from viral- to metabolic-driven liver cancer and emphasize the importance of identifying and better understanding risk factors and targeted interventions.

PO2-15
Patients' first port of call: Primary care and HCC surveillance

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Background and aims:
Surveillance for hepatocellular carcinoma (HCC) in patients with cirrhosis has been demonstrated to improve overall survival, but remains underutilised in clinical practice. Identifying barriers to HCC surveillance is key to increasing surveillance uptake and implementation. This study aimed to evaluate clinician-level knowledge and ascertain barriers to HCC surveillance in patients with cirrhosis in primary care

Method:
An online survey was sent to 200 general practitioners (GPs) across northwest London. HCC knowledge was assessed using 8 patient vignettes. Multiple-choice questions using Likert scales were used to obtain clinician characteristics, current surveillance practices, barriers and attitudes towards surveillance, and knowledge around screening modalities. Descriptive statistics, including frequency analysis and Chi-squared/Fisher-Exact tests, were undertaken.

Results:
A total of 187 primary care clinicians responded to the survey, of which 89 were suitable for analysis.
On HCC knowledge assessment, 76% of respondents achieved a score of 0-5, with 24% achieving a score of 6-8. Clinicians who saw more patients with cirrhosis (>50 compared to <25 per annum) scored higher in knowledge (p=0.035).

One third of clinicians usually ordered surveillance tests without discussing HCC surveillance in detail. Over half (54%) of clinicians stated that not being up to date with guidelines was a barrier to ordering surveillance. All respondents felt that HCC surveillance should be organised by gastroenterologists or hepatologists.

Clinicians desired more evidence regarding the benefits and harms of surveillance (87% and 79% respectively). Finally,100% of respondents thought that gastroenterologists and hepatologists +/- GPs should organise HCC screening.

Conclusion:
This is the first study assessing knowledge and identifying barriers to HCC surveillance amongst primary care in the UK. There are key knowledge gaps regarding HCC surveillance. The majority of primary care clinicians felt that a lack of knowledge about guidelines acted as a barrier to implementing surveillance. It is necessary to create an education programme around HCC surveillance and establish pathways between primary and secondary care for identification and referral of suitable patients, whilst determining which party ultimately bears the burden of responsibility for surveillance. This should be done in parallel to addressing patient- and system-level barriers to HCC surveillance to create a national surveillance programme.

PO3-8
Gaps remain in the cascade of hepatitis B care for people with HCC: a prospective cohort study

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Background and aims:
Hepatitis B (HBV) is a major cause of hepatocellular carcinoma (HCC) in Australia, despite availability of effective, subsidised treatment that reduces HCC risk. In this cohort study, we aimed to describe the clinical characteristics, cascade of HBV care and clinical outcomes among people with HBV-related HCC in Victoria, Australia.

Method:
We conducted a multi-centre retrospective (1st January 2018 to 31st Oct 2021) and prospective (1st Nov 2021 to 31st Oct 2022) cohort study of all incident HCC cases diagnosed across six tertiary health networks in Melbourne. HCC cases were identified through HCC multidisciplinary team (MDT) meetings, cross referenced with electronic medical records. Primary outcome was number (proportion) incident HBV-related HCC; secondary outcomes were number (proportion) HBV-HCC receiving guideline-based treatment and surveillance. Multivariable logistic regression modelling was used to determine variables associated with HBV treatment and surveillance uptake.

Results:
1203 incident HCC cases were identified, of which 219 (18.2%) were due to HBV. Over time, both the number and proportion of HCC cases due to HBV declined from 24% (N=52) in 2019 to 15% (N=33) in 2022. Most people with incident HBV- HCC were male (89%) and of Asian ethnicity (60%).

Cascade of HBV care: HBV status was known in all HBV-HCC cases at time of HCC diagnosis.

64% (141/ 219) had cirrhosis; 26% (57/ 141) were first diagnosed at HCC diagnosis. 60% of people with HBV-HCC (121 of 203 with available data) were eligible for HBV treatment at HCC diagnosis, yet 27% (22 / 121) were not on treatment. On multivariable analysis, referral from primary care (adjOR 0.18, 95% CI 0.03-0.96, p=0.04) and being admitted to hospital at HBV-HCC diagnosis (adjOR 0.09, 95% CI 0.02-0.34, p<0.001) were associated with not receiving guideline-based HBV treatment.

92% (201/ 219) of people with HBV-HCC were eligible for surveillance at the time of HCC diagnosis. Of these, 46% (N=92) were enrolled in surveillance (at least one surveillance ultrasound <12months of HCC diagnosis): 65% (72/103) referred by specialist hepatology services compared to 25% (21/ 91) referred by non-liver specialists (p<0.001).

Conclusion:
The proportion of incident HCC cases due to HBV is reducing in Victoria, however many people with HBV-related HCC are not receiving guideline-based care. Greater investment in education and training in HBV care, coupled with a national system to support HCC surveillance are urgently needed.

PO4-6-YI
Clinician-reported bias and stigma as barriers to HCC surveillance provision in the United Kingdom

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Background and aims:
Hepatocellular carcinoma (HCC) is the third-highest cause of cancer-related mortality worldwide. The majority of HCC cases are diagnosed at a late stage and are not amenable to curative treatment; thus HCC prognosis remains poor with a 5 year survival less than 20%. Biannual ultrasound surveillance for HCC in patients with cirrhosis is recommended by international professional bodies.

Previous studies in American and Asian cohorts suggest fewer than 25% of patients receive surveillance at recommended intervals; our multi-centre study of surveillance uptake in the United Kingdom found 16.5% regular attendance at surveillance. This study to explore barriers faced by clinicians in providing HCC surveillance within the United Kingdom's National Health Service (NHS).

Method:
A qualitative study was undertaken using semi-structured interviews with healthcare professionals involved in organising HCC surveillance. Participants were selected from across the UK using purposive and snowball sampling. Participants discussed their experiences of, and opinions on, HCC surveillance. All interviews were recorded and transcribed and analysed using thematic analysis.

Results:
16 healthcare professionals (n=12 consultant gastroenterologist/hepatologist, n=3 gastroenterology/hepatology registrar, n=1 prescribing pharmacist) were interviewed between October 2023 and January 2024. Participants were interviewed until thematic saturation was achieved.

Four themes were identified: (1) Guidelines: “weak evidence informed by opinion”; (2) Stigma: the deserving vs the undeserving sick; (3) An NHS in crisis, and (4) "It's all in the selling".

Conclusion:
This is the first study to explore barriers faced by clinicians in providing HCC surveillance within a national health service. Clinicians providing HCC surveillance describe key barriers to surveillance uptake and implementation. Working within a constrained national health service results in the belief systems are destined to fail, with system barriers, including IT and radiology capacity, being insurmountable. However, some barriers, including stigma towards patients with cirrhosis and scepticism about the evidence base for surveillance, are intrinsically held by clinicians. Addressing these barriers is likely to require significant cultural changes within the profession.

PO4-14-YI
Global trends in liver cancer attributable to Hepatitis B: Insights from the Global Burden of Disease 2023 Study

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Background and aims:
HBV-related liver disease ranks as the seventh leading cause of mortality. Despite advances in prevention and treatment, global disparities in the burden of primary liver cancer (PLC) persist. We evaluate global trends in the prevalence, incidence, and disability-adjusted life years (DALYs) of HBV-related liver disease.

Method:
We used the GHDx platform to access the Liver Cancer Attributable to Hepatitis B GBD database. We calculated incidence, prevalence, and disability-adjusted life years (DALYs) with 95% uncertainty intervals (UI) to assess the liver cancer burden worldwide. Metrics were reported as absolute numbers and rates per 100,000 population. Age-standardized percent changes (2000–2023) were calculated for prevalence (ASP), incidence (ASI), and DALYs (AS-DALYs). All of the analyses and visualizations were conducted using R (v4.3).

Results:
According to the Global Burden of Disease (GBD) 2023 data, the **global prevalence of liver cancer attributable to hepatitis B** has shown a **gradual decline** between 2000 and 2023. The **age-standardized prevalence rate** decreased from approximately **15 per 100,000 population in 2000** to about **11 per 100,000 in 2023**, representing a **reduction of nearly 25%** over the study period. The decline was most pronounced after 2010, coinciding with the expansion of **hepatitis B vaccination programs**, **antiviral therapies**, and **improved surveillance systems**. Despite this progress, the prevalence remains disproportionately high in **East and Southeast Asia**, regions historically affected by endemic hepatitis B virus infection. The overall pattern mirrors the reductions observed in both **incidence** and **DALYs**, indicating a consistent global improvement in disease control and long-term outcomes.

Conclusion:
The global burden of HBV-related liver cancer has markedly declined due to vaccination and antiviral programs, yet it remains a major challenge in low-resource regions. Sustained vaccination, expanded treatment access, and stronger surveillance are crucial to meet the WHO 2030 elimination goals.

PO6-9-YI
Global Burden of Hepatitis B–Attributable Liver Cancer in West and Central Africa, 2000–2023: Trends in Incidence, Prevalence, and Mortality

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Background and aims:
HBV-related liver disease ranks as the seventh leading cause of mortality. Despite advances in prevention and treatment, global disparities in the burden of primary liver cancer (PLC) persist. We evaluate trends in the prevalence, incidence, and deaths of HBV-related liver cancer in West and Central Africa.

Method:
We used the GHDx platform to access the Liver Cancer Attributable to Hepatitis B GBD database. We calculated incidence, prevalence, and mortality with 95% uncertainty intervals (UI) to assess the Liver cancer burden. Metrics were reported as absolute numbers and rates per 100,000 population. Age-standardized percent changes (2000–2023) were calculated for prevalence (ASP), incidence (ASI), and Deaths. All the analyses and visualizations were conducted using R (v4.3).

Results:
In 2023, liver cancer linked to hepatitis B showed the highest age-standardized incidence in Cameroon (7.6 per 100,000) and Senegal (6.5), followed by Nigeria (6.2), Ghana (5.0), and Uganda (2.6). A similar pattern appeared for prevalence, with Cameroon (8.8) and Senegal (7.8) leading, and Nigeria (6.9), Ghana (6.0), and Uganda (3.5) following. In all countries, prevalence exceeded incidence, suggesting delayed detection or longer survival among patients. Regional variability was notable, particularly in Cameroon, which had the widest uncertainty range (4.5–12.1).

Between 2000 and 2023, all five countries saw declines in age-standardized mortality rates. Nigeria achieved the greatest reduction (41.8%), followed by Ghana (32.1%) and Cameroon (25.1%), while Uganda (18.7%) and Senegal (7.7%) showed smaller decreases. Despite these improvements, hepatitis B–related liver cancer remains a major public health issue, with Nigeria, Cameroon, and Ghana accounting for the highest mortality burden in 2023.

Conclusion:
Liver cancer from hepatitis B remains a major problem in West and Central Africa especially in Cameroon, Senegal, and Nigeria due to delayed diagnosis and chronic infections. Despite some decline in deaths, the burden is still high, highlighting the need for stronger prevention, screening, and treatment efforts.

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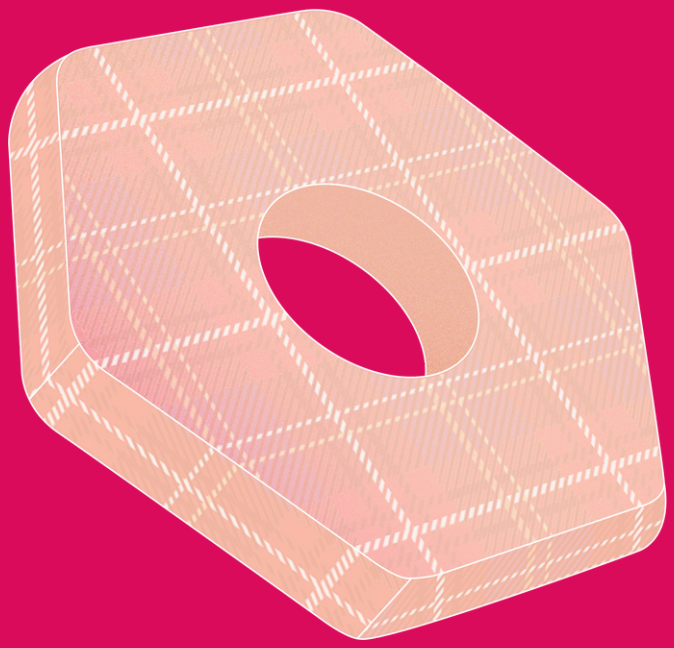

ABSTRACT BOOK

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