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Abstracts

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Divergent Chromosomal Architectures in Cholangiocarcinoma Cell Lines with Comparable Proliferation Rates: Implications for Genomic Heterogeneity

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Background: Cholangiocarcinoma (CCA) is highly aggressive with limited therapeutic options. While genomic and molecular profiling has advanced understanding of oncogenic drivers, genome-level mechanisms underlying resistance remain unclear. Chromosomal instability (CIN), characterized by ongoing numerical and structural aberrations, is a hallmark of advanced solid tumors and pivotal keys for enhancing prognostic accuracy and precision therapies.

Methods: Two Thai cholangiocarcinoma cell lines, KKU-M139 and KKU-M156, were analyzed. Growth kinetics were assessed over 12 days under identical conditions. Cytogenetic analysis utilized standard G- and C-banding. At least 50 metaphase spreads per line were examined; karyotypes were described per ISCN guidelines. Chromosomal number, ploidy status, and structural abnormalities were evaluated to assess CIN.

Results: KKU-M139 and KKU-M156 exhibited comparable doubling times (~7 days) but distinct chromosomal architectures. KKU-M139 displayed a hyperdiploid aneuploid karyotype (range: 65-92; mode: 74). In contrast, KKU-M156 exhibited a near-tetraploid karyotype (range: 102-157; mode: 124) with extensive structural rearrangements and pronounced CIN.

Conclusion: Findings demonstrate that chromosomal instability and ploidy status, rather than proliferation rate alone, define CCA genome architecture. Near-tetraploidy and severe CIN may underlie tumor heterogeneity, immune escape and drug resistance. Conventional cytogenetic profiling remains valuable for interpreting therapeutic resistance and selecting appropriate experimental models in translational research.

The Impact and Mechanisms of YES1 in Intrahepatic Cholangiocarcinoma Progression

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Background: Intrahepatic cholangiocarcinoma (ICC) incidence is rising, yet its molecular drivers remain incompletely defined. This study investigated the role of the Src family tyrosine kinase YES1 in ICC progression and its underlying mechanisms.

Methods: Tumor specimens from 130 ICC patients were subjected to next generation sequencing; YES1 was identified as a recurrently altered gene. NF1 expression changes were validated by qPCR and Western blot. Wild-type YES1 (YES1WT) and the YES1Y426A mutant were expressed in ICC cell lines; effects on proliferation, migration, apoptosis, and cell cycle were evaluated using CCK8, colony formation, EdU, Transwell, and wound-healing assays. YES1 knockdown and overexpression models were tested in vitro and in subcutaneous xenografts. Protein mass spectrometry and coimmunoprecipitation were performed to assess YES1/EGFR interactions. An orthotopic murine ICC model was used to evaluate dasatinib (YES1 inhibitor) and gefitinib (EGFR inhibitor).

Results: YES1 activity was found to promote ICC cell proliferation and migration. YES1wt enhanced EGFR phosphorylation and activated downstream PI3K/AKT and MAPK/ERK signaling. The YES1Y426A mutation disrupted YES1/EGFR phosphorylation, attenuating PI3K/AKT and MAPK/ERK pathway activation and suppressing tumorigenic phenotypes. Treatment with dasatinib or gefitinib reduced YES1/EGFR phosphorylation and downstream signaling, inhibiting tumor growth in the orthotopic model.

Conclusion: YES1 drives ICC progression via YES1/EGFR-mediated activation of PI3K/AKT and MAPK/ERK pathways. The YES1Y426A mutation impairs this axis, and pharmacologic inhibition of YES1 or EGFR suppresses ICC development. YES1 is thus proposed as a potential biomarker and therapeutic target in ICC.

Keywords: Intrahepatic cholangiocarcinoma, YES1, EGFR, PI3K/AKT, MAPK/ERK

Clinicopathological Features of Metabolic Dysfunction-Associated Steatotic Liver Disease-Related Intrahepatic Cholangiocarcinoma

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Objective: The association between metabolic dysfunction-associated steatotic liver disease (MASLD) and intrahepatic cholangiocarcinoma (ICC) remains understudied. This study aimed to report the clinical and pathological characteristics and prognosis of MASLD-ICC based on a retrospective analysis.

Methods: We conducted a single-center retrospective study including patients diagnosed with MASLD-ICC at Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, from January 2015 to October 2025. Diagnosis adhered to the 2024 EASL/EASD/EASO guidelines for MASLD and mainstream ICC guidelines. After screening, 9 eligible patients were included.

Results: The cohort comprised 9 middle-aged to elderly patients (age range 49 to 71 years) with a balanced sex ratio; none had a history of smoking or alcohol use. Concurrent HBV infection was present in 55.6% of cases. Pathologically, all tumors were mass-forming adenocarcinomas, predominantly poorly differentiated (66.7%) and of the small bile duct type (55.6%). Background liver pathology showed mild-to-moderate steatosis (77.8%) and varying degrees of fibrosis. The 1-year, 3-year, and 5-year overall survival rates were 100%, 88.9%, and 53.3%, respectively.

Conclusion: MASLD-ICC exhibits unique clinicopathological features, and its development may involve interactions between metabolic dysfunction, chronic inflammation, and HBV infection. This study provides the first systematic report of MASLD-ICC meeting the latest diagnostic criteria, suggesting a relatively favorable prognosis. However, due to the small sample size, further validation through multi-center studies is necessary to inform clinical strategies.

Prognostic Impact of Etiologies on Intrahepatic Cholangiocarcinoma: An Analysis of a Nationwide Registry

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Background: Chronic viral hepatitis is a recognized risk factor for intrahepatic cholangiocarcinoma (ICC); however, its prognostic significance remains controversial.

Methods: Using a nationwide Japanese registry, we identified patients newly diagnosed with ICC between 2018 and 2023. Patients were categorized into resection and non-resection cohorts according to initial treatment. Those with Child-Pugh C or distant metastasis were excluded from the resection cohort. The association between etiology (HBV, HCV, or non-B, non-C) and overall survival (OS) was evaluated using multivariable Cox proportional hazards models adjusted for demographic, liver function, and tumor-related variables.

Results: We analyzed 1,098 resection and 787 non-resection patients. Non-B, non-C etiology accounted for over 80% of cases. HBV-infected patients were younger in both cohorts. Tumor burden was similar among etiologies in the resection cohort, whereas in the non-resection cohort, HCV-related ICC showed smaller tumor size and a higher frequency of solitary lesions. Median OS was 62.6 months (resection) and 8.7 months (non-resection). In multivariable models, etiology was not significantly associated with OS in either cohort (resection: HBV vs. non-B, non-C: HR 0.78, p=0.42; HCV vs. non-B, non-C: HR 0.83, p=0.38; non-resection: HBV vs. non-B, non-C: HR 0.90, p=0.66; HCV vs. non-B, non-C: HR 1.06, p=0.73). Age, Child-Pugh class, and tumor characteristics were independently associated with OS.

Conclusion: Prognosis did not differ significantly by etiology regardless of resectability. In the contemporary antiviral era, liver function and tumor burden appear to be the dominant determinants of survival in ICC.

Dose-response Association between Waist Circumference and Risk of Cholangiocarcinoma: A Nationwide Population-based Cohort Study

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Background: Waist circumference (WC) is a well-established indicator of visceral adiposity and metabolic risk, but its dose-response relationship with cholangiocarcinoma (CCA) has not been clearly defined. This study evaluated the association between WC and the risk of CCA.

Methods: This population-based study included 4,454,232 cancer-free adults who underwent the 2012 Korean National Health Screening. A random 40% sample was analyzed. WC was categorized into six groups, with abdominal obesity defined as WC 90 cm or greater in men and 85 cm or greater in women based on Korean criteria. Participants were followed until December 2023. Multivariable Cox proportional hazards models were used to estimate the risk.

Results: Over a median follow-up of 10.3 years, 8,902 cases of CCA were identified. Compared with individuals with WC of 85.0 to 89.9 cm in men and 80.0 to 84.9 cm in women, those with lower WC (less than 80.0 cm in men and less than 75.0 cm in women) had significantly reduced risks of intrahepatic and extrahepatic CCA (adjusted hazard ratios, 95% CIs: 0.91, 0.85 to 0.99 and 0.79, 0.73 to 0.86, respectively). In contrast, participants with WC 100.0 cm or greater in men and 95.0 cm or greater in women showed increased risks of these cancers. The associations were consistent across most subgroups.

Conclusion: WC showed a clear dose-response association with the risk of CCA, with lower WC associated with reduced risk and higher WC with increased risk, suggesting that abdominal obesity reduction may help lower the incidence of these malignancies.

Clinical Utility of Peroral Cholangioscopy-Guided Biopsy in the Diagnosis of Biliary Lesions

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Background: Peroral cholangioscopy (POCS) is increasingly used for indeterminate biliary lesions. However, its diagnostic value has not yet been fully established.

Methods: We retrospectively analyzed 91 consecutive patients who underwent POCS-guided biopsy for indeterminate biliary lesions at our institution between April 2014 and May 2024. The final diagnosis was determined based on histopathological findings or clinical diagnosis established at 6 months of follow-up. Outcomes included technical success rate, diagnostic accuracy, and procedure-related adverse events.

Results: The mean age was 73.8 years, and 58 patients were male. Lesions were located in intrahepatic bile duct (n=14), hilar bile duct (n=34), distal bile duct (n=30), gallbladder including the cystic duct (n=10), anastomotic site (n=2), and the entire bile duct (n=1). The technical success rate was 94.5% (86/91). Excluding 2 patients with undetermined final diagnoses, 84 patients were included in the diagnostic analysis; 49 (58.3%) had neoplastic and 35 (41.7%) had non-neoplastic lesions. The overall diagnostic accuracy of POCS-guided biopsy was 79.8%, with a sensitivity of 65.3% and a specificity of 100%. Diagnostic accuracy was significantly higher when using the SpyBite MAX biopsy forceps compared with conventional forceps (95.8% vs. 71.4%, $p = 0.03$). Multivariate logistic regression identified the use of SpyBite MAX as the only independent factor associated with correct diagnosis (odds ratio 9.80; 95% C.I. 1.65-190.2; $p=0.008$). Procedure-related adverse events occurred in 8 patients and were all managed conservatively.

Conclusions: POCS-guided biopsy is a safe and effective diagnostic modality for indeterminate biliary lesions. The use of novel biopsy forceps significantly improves diagnostic accuracy.

Optimal Biliary Drainage for Malignant Hilar Biliary Obstruction

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Aim: With the introduction of immune checkpoint inhibitor (ICI) therapy, survival outcomes for unresectable or recurrent biliary tract cancer have improved. Consequently, biliary drainage strategies that consider reintervention (RI) have gained importance, and treatment choices have been shifting from metal stents (MS) emphasizing long-term patency to removable plastic stents (PS). This study evaluated the optimal biliary drainage strategy for malignant hilar biliary obstruction.

Methods: Among 205 patients with unresectable advanced biliary tract cancer treated with GemCis(GC) or GC+ICI between January 2011 and December 2024, 60 patients who underwent endoscopic biliary drainage for hilar obstruction were included. Patients were classified into an MS group (n=38) and a PS group (n=22). Outcomes including recurrent biliary obstruction (RBO), time to RBO (TRBO), adverse events, total number of RIs, conversion to PTBD/EUS-guided biliary drainage (EUS-BD), antitumor response, and overall survival (OS) were compared. Stents were exchanged on an on-demand basis.

Results: Baseline characteristics were comparable between groups. Although stent configuration and number differed, technical and clinical success rates, adverse events, drained liver volume, total RI number, and PTBD/EUS-BD conversion rates were similar. The MS group more frequently received GC and demonstrated significantly longer TRBO (6.9 vs. 2.3 months, $p<0.01$) and OS (13.0 vs. 10.8 months, $p=0.04$). Early cholangitis within 3 months after drainage was associated with poorer OS and increased RI frequency, regardless of stent type.

Conclusions: With an on-demand exchange strategy, MS provided superior outcomes compared with PS. Preventing early post-drainage cholangitis may be critical for improving survival and reducing reinterventions.

Selective Endoscopic Nasobiliary Drainage to Determine the Resection Range for Intraductal Papillary Neoplasm of the Bile Duct with an Indeterminate Primary Site: A Case Report

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Introduction: Intraductal papillary neoplasm of the bile duct (IPNB) is a rare precursor to cholangiocarcinoma, often characterized by significant mucin hypersecretion.

Case Presentation: An 83-year-old female with a four-year history of asymptomatic biliary dilation presented with acute fever and obstructive jaundice (total bilirubin 5.8 mg/dL, C-reactive protein 17 mg/dL). Although magnetic resonance and endoscopic retrograde cholangiopancreatography demonstrated marked bilateral bile duct dilation and viscous bile, initial imaging failed to localize the tumor; positron emission tomography-CT was also negative. A second peroral cholangioscopy successfully identified a papillary tumor distal to the confluence of segments 2 and 3 (B2/3). To differentiate between diffuse neoplastic involvement and secondary mucin-induced dilation of the right liver, an endoscopic nasobiliary drainage tube was selectively placed in the right hepatic duct. The subsequent drainage of normal-colored, non-viscous bile and the resolution of jaundice confirmed that the right-sided dilation was caused by mucin reflux from the left liver. Clinical assessments, including an indocyanine green retention test at 15 minutes of 8.2%, a right liver biopsy (Metavir score F2), and a future liver remnant volume of 74%, indicated sufficient functional reserve.

Management and Outcome: The patient underwent a left hepatectomy, including the caudate lobe. Histopathological examination confirmed type 1 IPNB with high-grade atypia (carcinoma in situ) and negative surgical margins. The postoperative course was uneventful.

Conclusion: This case underscores the utility of cholangioscopy and selective biliary drainage in accurately determining the surgical extent for mucin-producing IPNB, ensuring a curative (R0) resection while preserving adequate liver volume in elderly patients.

Case Report of Primary Hepatic Carcinoma Complicated with Cholangiolar Sarcomatoid Carcinoma

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Objective: To report an extremely rare case of primary hepatic carcinoma (PHC) complicated with cholangiolar sarcomatoid carcinoma (CSC) and provide valuable clinical reference for the diagnosis and treatment of such rare entities.

Case Summary: A 65-year-old male farmer with chronic hepatitis B, hypertension, type 2 diabetes and coronary heart disease was admitted in May 2019 due to intermittent epigastric pain for 3+ months. Laboratory tests showed positive HBV markers, elevated HBV DNA, ALT and AST. Contrast-enhanced imaging revealed a 24*19 mm hyperechoic mass in the right anterior liver lobe, confirming PHC (CNLC Ia). Radiofrequency ablation (RFA) with water-isolation technique and entecavir antiviral therapy were performed, with stable lesions postoperatively. In December 2023, he developed lumbodorsal pain; imaging indicated portal vein thrombosis and extrahepatic metastasis (CNLC IIIb). Sintilimab + bevacizumab (first-line) relieved pain. Subsequent disease progression (PD) led to regimen adjustments (sintilimab + apatinib, then apatinib monotherapy due to immune-related dermatitis). Notably, in June 2025, the patient presented with fever, abdominal pain and jaundice; MRCP suggested cholangiocarcinoma, and ERCP stenting failed to resolve fever. Needle biopsy of neck lymph nodes finally confirmed the rare coexistence of cholangiocellular carcinoma with sarcomatoid change (CSC) in this PHC patient.

Conclusion: The coexistence of PHC and CSC is extremely rare, characterized by complex clinical manifestations and poor prognosis. Multidisciplinary diagnosis and treatment (MDT) and close follow-up are crucial for formulating and adjusting individualized therapy for such rare cases.

Advances in the Management of Intrahepatic Cholangiocarcinoma and Temporal Changes in Prognosis: A Prospective Long-Term Real-World Data Analysis

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Background: Yamanashi Prefectural Central Hospital is one of the 51 designated cancer care hospitals in Japan. Since 2006, 26,783 cases across 25 cancer types have been prospectively registered in our institutional database, with a confirmed vital status rate exceeding 95%. Using this real-world database, we investigated temporal changes in treatment outcomes for intrahepatic cholangiocarcinoma (ICC).

Methods: Patients diagnosed with ICC between January 2007 and December 2025 were included. According to the year of diagnosis, patients were classified into an early period (2007–2016) and a late period (2017–2025). Overall survival (OS) was evaluated using the Kaplan–Meier method and compared between periods for each disease stage.

Results: Median overall survival (MST) by stage and period was as follows: Stage I, 32.8 months in the early period, while the MST was not reached in the late period; Stage II, 17.7 months in the early period and 81.2 months in the late period ($p < 0.001$); Stage III, 8.1 months and 3.2 months; and Stage IV, 4.3 months and 6.6 months, respectively. In the late period, long-term survivors increased in Stage I, and a significant survival benefit was observed in Stage II. In contrast, no improvement was observed in Stage III, and prognosis remained poor in Stage IV.

Conclusions: Outcomes for ICC have improved over time in a stage-dependent manner, particularly in Stage I–II disease. However, outcomes for advanced ICC remain unsatisfactory, underscoring the need for further optimization of multidisciplinary treatment strategies.

Hepatic Arterial Infusion Chemotherapy with New FP (NFP) for Unresectable Intrahepatic Cholangiocarcinoma: A Single-Center Retrospective Study

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Background: Gemcitabine plus cisplatin (GC) is standard chemotherapy for unresectable intrahepatic cholangiocarcinoma (iCCA), but outcomes remain suboptimal. We compared a Lipiodol-based hepatic arterial infusion chemotherapy (HAIC), New FP (NFP), with GC for unresectable iCCA.

Methods: We retrospectively enrolled patients with unresectable iCCA treated between March 2015 and March 2023. NFP comprised cisplatin 50 mg suspended in 5-10 mL Lipiodol on days 1 and 8, followed by 5-fluorouracil 1500 mg every 2 months. Tumor response was assessed by RECIST; discontinuation due to adverse events (AEs) was recorded.

Results: Thirty patients were included (NFP/GC, 15/15). Median age was 70/67 years and 12/8 were male; stage (III/IV/postoperative recurrence) was 9/5/1 vs 8/7/0. Prior therapy occurred only in the NFP group (gemcitabine-based, n=4; S-1, n=1). Best response (PR/SD/PD) was 5/8/2 with NFP and 1/8/6 with GC; disease control rate was 86.7% vs 60.0%. NFP achieved a higher PR rate (33.3% vs 6.7%, $p=0.0374$) and greater median tumor shrinkage (32.9% vs -0.9%, $p=0.000021$). AE-related discontinuation occurred in 4/15 with NFP and 10/15 with GC ($p=0.0282$); in the NFP group, discontinuations included renal dysfunction (n=2; after 4 or 6 courses) and biloma (n=1; after 5 courses).

Conclusion: NFP demonstrated favorable local efficacy with fewer AE-related discontinuations than GC in unresectable iCCA. Larger studies and prospective trials, including combinations with systemic chemotherapy and immune checkpoint inhibitors, are warranted.

Analysis of Prognostic Factors for ICI Combination Regimens in Unresectable Biliary Tract Cancer

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Background: Based on survival benefits shown in the TOPAZ-1 and KEYNOTE-966 trials, gemcitabine plus cisplatin (GC) combined with immune checkpoint inhibitors (ICI) has become standard for unresectable biliary tract cancer. However, differences between durvalumab and pembrolizumab and the safety of ICIs in elderly patients or those with biliary drainage remain unclear.

Methods: This retrospective study analyzed 26 patients treated with GC+ICI from April 2022 to September 2025.

Results: Median age was 73 years; 57.7% were male. Primary tumors included intrahepatic cholangiocarcinoma (n=8), hilar cholangiocarcinoma (n=6), gallbladder cancer (n=11), and unknown primary (n=1). Durvalumab was used in 18 patients and pembrolizumab in 8. Median follow-up was 214 days. The overall response rate was 28.6%, disease control rate 90.5%, and 29.2% transitioned to ICI maintenance therapy. Immune-related adverse events (irAEs) occurred in 23.1%, significantly more frequent with pembrolizumab than durvalumab (50.0% vs. 11.1%, p=0.04). Median progression-free survival (PFS) was 8.2 months with durvalumab and 8.9 months with pembrolizumab, showing no significant difference (p=0.88). Age>75 years was a significant poor prognostic factor for PFS (HR 4.55; 95% CI, 1.26-18.3; p=0.02), while ICI regimen and biliary drainage were not.

Conclusion: These results suggest comparable efficacy between durvalumab and pembrolizumab, with potentially lower irAEs incidence for durvalumab. GC+ICI therapy may be less effective in elderly patients, warranting careful consideration of treatment appropriateness.

Immune Checkpoint Inhibitors Combined with Chemotherapy and Comprehensive Genomic Profiling Test for Advanced Biliary Tract Cancer in Our Hospital

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Background: Immune checkpoint inhibitors (ICIs) have recently been incorporated into first-line treatment for advanced biliary tract cancer (BTC) in Japan, with gemcitabine-cisplatin-durvalumab (GCD) and gemcitabine-cisplatin-pembrolizumab (GCP) becoming standard regimens. However, real-world evidence regarding their efficacy, safety, and subsequent treatment strategies, including comprehensive genomic profiling (CGP), remains limited. This study evaluated real-world outcomes of GCD and GCP and assessed the clinical utility of CGP in later-line decision-making.

Methods: We retrospectively analyzed 40 patients with unresectable or recurrent BTC who received GCD or GCP between July 2023 and March 2025. In addition, 21 patients who underwent CGP testing between August 2021 and March 2025 were evaluated.

Results: The median age was 73 years (range, 40-83). Primary tumor sites included intrahepatic bile duct (n=15), extrahepatic bile duct (n=14), and gallbladder (n=11). GCD and GCP were administered in 32 and 8 patients, respectively. The best overall responses were CR/PR/SD/PD in 1/13/21/5 patients, yielding an objective response rate of 35.0% and a disease control rate of 87.5%. Median progression-free survival and overall survival were 245 and 653 days, respectively. Immune-related adverse events occurred in 7.5% (3/40), with no treatment-related deaths. CGP identified actionable genomic alterations or biomarkers in 33% (7/21), predominantly in intrahepatic cholangiocarcinoma. The treatment access rate was 14%, limited mainly by trial availability.

Conclusions: Although limited by its single-center, small-sample design, this study suggests that both GCD and GCP are safe and effective in real-world BTC. Given the relatively high rate of actionable findings, proactive CGP testing is warranted.

The Impact of Antibiotics on ICI Combination Chemotherapy in Advanced Biliary Tract Cancer

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Background: Antibiotic use has been reported to potentially reduce the efficacy of immune checkpoint inhibitors (ICIs) in various malignancies; however, its impact in biliary tract cancer (BTC) remains unclear.

Methods: This retrospective single-center cohort study included 42 patients with advanced BTC who underwent first-line ICI combination chemotherapy - gemcitabine plus cisplatin with durvalumab (GCD) or pembrolizumab (GCP) - between January 2023 and June 2025. Progression-free survival (PFS), overall survival (OS), and tumor response were compared among the three groups based on antibiotic use: prophylactic-user (n=20), treatment-user (n=18) and non-user (n=4). The impact of antibiotic use on PFS and OS was evaluated using a Cox proportional hazards model.

Results: Baseline characteristics were generally comparable across the three groups, except for primary tumor site and disease stage. Median PFS in prophylactic-users, treatment-users, and non-users was 304, 393, and 511 days, respectively (p=0.04), while median OS was not reached, 494 days, and not reached, respectively (p=0.22). Response rates were 25%, 30%, and 22%, respectively (p=0.88). In multivariate analysis, antibiotic use was not identified as an independent factor associated with PFS or OS; the hazard ratios for prophylactic and treatment use were 1.40 (95% CI, 0.24-8.30) and 1.25 (95% CI, 0.23-6.78) for PFS, and 1.87 (95% CI, 0.16-22.27) and 1.48 (95% CI, 0.16-14.00) for OS, respectively.

Conclusion: Antibiotic use was not associated with a negative impact on the efficacy of ICI combination chemotherapy in patients with advanced BTC.

Two Cases of Unresectable Combined Hepatocellular-Cholangiocarcinoma Treated with Immune Checkpoint Inhibitors

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Background: Combined hepatocellular-cholangiocarcinoma (cHCC-ICC) is a rare primary liver cancer, accounting for <1% of cases in a national survey in Japan. It shows histological heterogeneity and overlapping features of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Because imaging, pathology, and tumor markers often provide discrepant information, diagnosis and treatment selection are complex. Evidence for immune checkpoint inhibitors (ICIs) in cHCC-ICC remains scarce.

Methods: We report two patients with unresectable cHCC-ICC treated with ICI based regimens. Case 1: an 81 year old man with stage IVa cHCC-ICC, with portal vein tumor thrombus (Vp3). AFP and DCP were markedly elevated, while CEA and CA19-9 were normal. Histology showed cholangiolocellular and poorly differentiated adenocarcinoma components. SBRT for PVTT was followed by Durvalumab plus Tremelimumab. Case 2: a 72 year old woman with stage IVb cHCC-ICC, with extensive lymph node metastases. AFP and DCP were elevated, with mildly increased CEA and CA19-9. Histology demonstrated intermediate hepatocellular-cholangiocellular phenotype. She received Atezolizumab plus Bevacizumab.

Results: Both patients achieved responses. In Case 1, AFP and DCP declined, the main lesion regressed, and PVTT decreased in size and remained reduced. In Case 2, AFP showed a marked decline and DCP normalized after five courses, with partial response. No severe immune related adverse events occurred.

Conclusions: ICI based therapy can induce responses in unresectable cHCC-ICC. Tumor markers guided treatment choice, but their predictive value remains uncertain. Further accumulation of case experiences and collaborative data is essential to clarify optimal management strategies for this rare entity.

SLC12A2-driven Suppression of Hepatic Lipolysis Shapes a Tumor-promoting Microenvironment in Metabolically Steatotic Livers

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Background: Hepatocellular carcinoma (HCC) frequently develops in steatotic and fibrotic livers. Although multiple factors have been implicated, the molecular mechanisms that shape a tumor-promoting hepatic microenvironment in metabolically compromised livers are not fully understood. We examined whether hepatic expression of the Na⁺-K⁺-Cl⁻ cotransporter SLC12A2 is associated with HCC risk and steatohepatitis-related carcinogenesis.

Methods: Six hundred seventeen hepatic transporter genes were screened for prognostic relevance in a publicly available transcriptomic HCC cohort. Hepatic SLC12A2 mRNA was quantified by RNA sequencing in a biopsy-based cohort of 94 patients with metabolic dysfunction-associated steatotic liver disease (MASLD), including 12 with HCC. Functional studies used C57BL/6 mice with hepatic SLC12A2 overexpression via AAV8 and a choline-deficient, L-amino acid-defined, high-fat diet, and in vitro models of hepatic cell lines with stable SLC12A2 overexpression or shRNA knockdown.

Results: SLC12A2 showed the highest hazard ratio for survival among transporters and was associated with increased late (>2 years) post-hepatectomy recurrence. In the MASLD cohort, hepatic SLC12A2 expression was higher in HCC cases and positively correlated with fibrosis stage and liver stiffness. In mice, SLC12A2 overexpression aggravated steatohepatitis, increasing liver weight, serum ALT, hepatic triglycerides, fibrosis, apoptosis, and compensatory proliferation, and yielded larger orthotopic tumors. In vitro, SLC12A2 promoted palmitate-induced lipid droplet accumulation while reducing glycerol release, indicating impaired lipolysis without major changes in fatty acid genes.

Conclusions: SLC12A2 promotes hepatic steatosis and a tumor-promoting microenvironment by suppressing lipolysis. Hepatic SLC12A2 overexpression identifies MASLD livers at high risk for HCC and represents a potential therapeutic target in metabolic liver disease-associated hepatocarcinogenesis.

Accumulation of Autophagy-specific Substrate p62/SQSTM1 is Associated with Multinucleation in Human Hepatocellular Carcinoma

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Background: Abnormally accumulated inclusions were observed in human hepatocellular carcinoma (HCC) cells in which autophagy-specific substrate p62/SQSTM1 was discovered to be the major component of these inclusions. We identified Importin- α 4, 14-3-3 ζ as insoluble nucleoproteins increased by autophagic dysfunction. We evaluated the relationship between the expression of these autophagy-related proteins and changes in nuclear morphology in hepatic cancer cells.

Methods: Sections from 12 surgically resected HCCs were analyzed by immunohistochemistry for p62/SQSTM1, Importin- α 4, and 14-3-3 ζ . The percentage of tumor cells showing p62-positive aggregates and nuclear staining for Importin- α 4 or 14-3-3 ζ was quantified in representative fields. Associations with platelet count, AST, ALT, γ -GTP, FIB-4 index, and fibrosis/inflammation scores in the non-tumor liver were assessed using Spearman's rank correlation. Multinucleated tumor cells were counted on H&E sections and correlated with protein expression.

Results: p62-positive aggregates were detected in all cases (57.9 \pm 10.4% of tumor cells). Nuclear Importin- α 4 and 14-3-3 ζ were also observed in all samples (79.0 \pm 4.7% and 42.9 \pm 6.4% of tumor cells, respectively). The extent of p62 aggregation was not associated with laboratory parameters, non-tumor fibrosis/inflammation, or nuclear 14-3-3 ζ . In contrast, nuclear Importin- α 4 significantly correlated with p62 aggregation. Multinucleated tumor cells observed 17.3 \pm 3.1% of cancer cells, were enriched among cells with p62 aggregation.

Conclusions: Human HCC commonly shows p62/SQSTM1-positive inclusions with nuclear Importin- α 4 accumulation, and correlates with multinucleation. Previous studies suggest that neoplastic multinucleation is associated with malignant transformation of cancer and induction of chemoresistance. Therefore, p62/SQSTM1 and Importin- α 4 might be useful biomarkers for evaluating the characteristics of HCC.

Investigation of the Anti-tumor and Anti-HBV Effects of the Host Factor FAH

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Background: Chronic hepatitis B is a major cause of hepatocellular carcinoma (HCC). We previously identified fumarylacetoacetate hydrolase (FAH) as a regulator of the HBV life cycle in primary human hepatocytes (PLoS ONE, 2025). In this study, we investigated whether FAH may exert both anti-tumor and anti-HBV effects.

Methods: FAH and Ki-67 were quantified by H-score using Inform software in tumor and non-tumor areas of 106 resected HCC specimens. The FAH index (tumor/non-tumor H-score) was analyzed for associations with recurrence and prognosis. HBV-stably transfected HepG2 clones with low (HepG2.1-E10) or high (HepG2.D11) HBV transcription were transfected with a FAH expression vector or FAH siRNA. Supernatant HBsAg, cell proliferation, apoptosis, and sphere formation were assessed. Transcriptome microarray analysis coupled with GSEA-based pathway analysis was performed to identify FAH-modulated pathways and genes.

Results: Tumor FAH was lower than non-tumor FAH (Δ H-score -10.99, $p < 0.01$) and inversely correlated with Ki-67 ($p < 0.01$). A low FAH index was associated with poorer recurrence ($p < 0.01$) and survival ($p < 0.05$). In both HBV-stably transfected clones, FAH overexpression decreased HBsAg, inhibited proliferation, increased apoptosis, and reduced sphere formation, whereas FAH knockdown produced reciprocal effects. GSEA showed that the WP Pluripotent stem cell differentiation pathway was suppressed by FAH overexpression, whereas it was enriched following FAH knockdown. In addition, expression of anti-HBV response-related genes (e.g., CGAS, IFNB1, IRF7, and OAS2) was increased.

Conclusion: FAH may contribute to anti-tumor and anti-HBV effects by suppressing stemness-related differentiation pathways and enhancing anti-HBV responses, supporting FAH as a potential therapeutic target in virus-associated hepatocarcinogenesis.

BEP1-4 10134

Ameliorative Role of Phytosterol Pre-Treatment in N-Nitrosodiethylamine Induced Oxidative Stress in Female Albino Rats

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N-Nitrosodiethylamine (NDEA) is a potent environmental carcinogen known to induce severe oxidative stress mediated hepatic and renal injury. This study aimed to evaluate the protective potential of phytosterol pre-treatment against NDEA induced oxidative damage in the liver and kidneys of female albino rats. Female Wistar rats were administered a single intraperitoneal necrogenic dose of NDEA (200 mg/kg body weight). Prior to NDEA exposure, animals received phytosterol pre-treatment via oral gavage at doses of 50 mg/kg or 100 mg/kg body weight, twice weekly for four weeks. Animals were sacrificed on days 7, 14, and 21 following NDEA administration. Hepatic and renal oxidative stress markers, antioxidant enzyme activities, serum biochemical parameters, and histopathological changes were assessed. NDEA exposure resulted in significant increases in hepatic lipid peroxidation, renal ornithine decarboxylase activity, urea, creatinine, and conjugated diene levels, accompanied by suppression of antioxidant defenses including superoxide dismutase, catalase, and total glutathione. Phytosterol pre treatment significantly attenuated oxidative stress markers and restored antioxidant enzyme activity in a dose- and time-dependent manner, with maximal protection observed on day 21. Serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase were markedly elevated following NDEA administration but were significantly reduced in phytosterol-treated groups, particularly at the higher dose. Histopathological evaluation demonstrated that phytosterol pre-treatment substantially improved NDEA induced renal structural damage. Phytosterol pre-treatment effectively mitigated NDEA induced oxidative stress and partially protected against hepatic and renal injury in female albino rats, supporting its potential role as a chemoprotective agent against carcinogen-induced organ toxicity.

Withdrawn

BEP2-2 10109

Multi-omics Profiling Reveals the Prognostic Features and Tumor Microenvironment of High-stemness HCC

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Background: The specific interaction between highly invasive hepatocellular carcinoma (HCC) and the tumor microenvironment (TME) is associated with poor prognosis and immune escape, and the outcome affects the efficacy of immunotherapy. Therefore, it is necessary to clarify the relationships among immunosuppressive subpopulations to provide promising treatment strategies.

Methods: In this study, scissor+ cell types associated with high-stemness HCC were screened by scissor analysis using single-cell datasets from HCC patients receiving immunotherapy. We developed and identified high-stemness HCC subtypes by performing a collaborative analysis of models from four independent cohorts using 12 machine learning algorithms combined with SHAP analysis. Subsequently, we analyzed the interaction between HCC subtypes and the immune microenvironment through CellChat and spatial transcriptomics.

Results: Highly stemness-associated gene (HSAG) were screened through differential analysis of scissor cell types, and the HSAG HCC subtypes were determined by machine learning combined with SHAP analysis. In addition, the HCC dataset was divided into two subtypes: the high HSAG HCC and the low HSAG HCC. In four independent HCC cohorts, high HSAG correlated with poor prognosis. Notably, CellChat analysis showed that high HSAG HCC interacted with SPP1+TMAs, and co-localization was verified in the spatial transcriptome of the non-immune response.

Conclusion: This study explored the subtypes of HCC patients associated with poor prognosis, providing insights into the interaction of the tumor microenvironment and prediction of patient prognosis.

ZIP1-CAF Shapes the Immunosuppressive Microenvironment to Drive Hepatocellular Carcinoma Progression

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Background: The stroma of hepatocellular carcinoma is primarily composed of cancer associated fibroblasts (CAF) and collagen. Interconnected CAFs form a robust immune effector barrier that not only promotes the exhaustion of anti-tumor immune cells but also recruits immunosuppressive cells, thereby driving tumor progression and metastasis. ZIP1 is a membrane protein responsible for zinc ion transport, and the high intracellular free zinc levels it mediates can activate multiple proliferation and cell activation pathways. However, how ZIP1 promotes CAFs activation and mediates CAFs driven remodeling of the HCC immune microenvironment remains unknown.

Methods: A combination of biological and informatics techniques was employed in this study.

Results: ZIP1 CAFs is significantly associated with poor prognosis in HCC. ZIP1 mediates the formation of myofibroblast like CAFs. ZIP1 CAFs reshapes the immunosuppressive microenvironment in HCC. ZIP1 inhibition enhances the efficacy of immunotherapy.

Conclusion: ZIP1 is a key regulator promoting CAF activation and extracellular matrix phenotype formation. ZIP1 CAF facilitates HCC progression by shaping an immunosuppressive microenvironment and reducing CD8 T cell infiltration. Targeting ZIP1 represents a promising strategy to improve the effectiveness of immunotherapy in hepatocellular carcinoma.

BEP2-4 10132

Microenvironmental Analysis of Resistance to Atezo+Bev Therapy in Unresectable Hepatocellular Carcinoma: Involvement of High M2BP Expression and Inflammatory Cancer-Associated Fibroblasts

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Background: Atezolizumab plus bevacizumab (Atezo+Bev) is the standard of care for unresectable hepatocellular carcinoma (HCC), yet approximately half of patients exhibit treatment resistance. We previously identified Mac2-binding protein (M2BP), produced by inflammatory cancer-associated fibroblasts (iCAFs), as a poor prognostic factor in pancreatic cancer. This study aimed to elucidate the role of M2BP-producing cells and their impact on the immune microenvironment in Atezo+Bev-resistant HCC using spatial transcriptomics.

Methods: We performed Visium spatial transcriptomic analysis on HCC tissues from 3 non-responders (PD) and 2 responders (1 SD, 1 CR) after Atezo+Bev therapy. We analyzed the spatial correlation between M2BP (LGALS3BP) expression and fibrosis-related genes, CAF markers, and T-cell exhaustion markers.

Results: M2BP expression was significantly higher in both tumor and adjacent liver tissues of non-responders. In these cases, high M2BP expression areas overlapped with increased expression of iCAF markers (IL6, CXCL1) and the iCAF activator CXCL10, suggesting a microenvironment of continuous fibroblast stimulation. These regions also showed high expression of COL1A1 and matrix metalloproteinases (MMPs), indicating active tissue remodeling and progressive fibrosis. Furthermore, CD8-positive T-cells in high M2BP regions significantly co-expressed exhaustion markers such as LAG3, indicating a potent immunosuppressive state.

Conclusion: In Atezo+Bev-resistant HCC, high M2BP expression is closely associated with iCAF-mediated progressive fibrosis and T-cell exhaustion. Targeting M2BP or iCAFs may represent a novel therapeutic strategy to overcome immunotherapy resistance in HCC.

Association of HAMP Expression and CD8+ T-cell Infiltration with Atezolizumab plus Bevacizumab Response in Hepatocellular Carcinoma

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Aim: Atezolizumab combined with bevacizumab is the first-line therapy for unresectable hepatocellular carcinoma; however, predictive biomarkers of therapeutic response remain undefined. We aimed to identify molecular features associated with therapeutic efficacy to develop personalized treatment strategies.

Methods: Transcriptomic analyses were performed using public RNA-sequencing datasets of patients with hepatocellular carcinoma receiving anti-PD-L1-based therapy, comparing responders (complete response/partial response) with non-responders (stable disease/progressive disease). Differentially expressed genes and enriched pathways were identified using differential expression and pathway analysis. For validation, RNA-sequencing was performed on institutional tumor samples (n=6) underwent. Immunohistochemistry was performed on resected specimens (n=9) to evaluate CD8+ tumor-infiltrating lymphocytes and hepcidin protein expression encoded by the HAMP gene. Group comparisons for the pre-specified immunohistochemistry endpoints were analyzed using exact Wilcoxon rank-sum tests with multiplicity control (Holm adjustment).

Results: Analysis of public datasets revealed distinct expression profiles in responders, enriched in immune-related and chemokine signaling pathways. Candidate genes, including HAMP, TAT, and HRG, were upregulated in responders. In institutional samples, HAMP expression was significantly higher in preoperatively treated tumors ($p=0.001$). Immunohistochemistry demonstrated greater CD8+ tumor-infiltrating lymphocyte density (median 36.6 vs. 5.0 cells/high-power field; exact Wilcoxon $p=0.032$) and higher HAMP immunoreactive scores (median 4 vs. 0.5; $p=0.032$) in responders than in non-responders.

Conclusions: Upregulation of HAMP and hepcidin protein expression, together with increased CD8+ T-cell infiltration, was associated with a favorable response to atezolizumab plus bevacizumab in patients with hepatocellular carcinoma. HAMP may serve as a component of a composite biomarker predictive of therapeutic sensitivity, warranting validation in larger, multi-institutional cohorts.

Mutation Profiles of TERT, TP53, and CTNNB1 Genes from Circulating Cell Free DNA as Non-Invasive Prognostic Biomarkers in HBV-Induced Hepatocellular Carcinoma

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Background: Chronic hepatitis B virus (HBV) infection is the major etiological agent of hepatocellular carcinoma (HCC) in Bangladesh. Somatic mutations in TERT, TP53 and CTNNB1 genes are frequently tied-up with hepatocarcinogenesis. Circulating cell free DNA (cfDNA) as liquid biopsy, is a promising non-invasive alternative of conventional biopsy material for detection of genetic alterations. This study aimed to detect these gene mutations from cfDNA of Bangladeshi HCC patients.

Materials and Methods: cfDNA was extracted from blood samples of 30 HCC patients and 20 healthy control. Amplification of the TERT promoter, TP53 and CTNNB1 genes were performed using selected primers via conventional PCR followed by gel electrophoresis and analyzed through Sanger sequencing, mutation analysis done by MEGA 11 software comparing with specific reference sequences.

Results: 40.0% (12/30) of HCC patients had hotspot mutations in TERT promoter (10%), TP53 (23.3%) and CTNNB1 (6.7%) genes. 6.7% (2/30) was detected at position c.146 (p.L250L) and 3.3% (1/30) at c.124 (p. P228L) of TERT gene. Highest mutation frequency was detected in TP53 with 13.3% (4/30) at position c.746 (p.G249S), 6.7% (2/30) at position c.735 (p.A245V) and 3.3% (1/30) at c.747 (p.G249V). The CTNNB1 gene showed 6.7% (2/30) mutation at position c.110 (p.S37Y) and c.133 (p.S45Thr). All mutations were strongly associated with low serum albumin (<3.4 g/dl) and elevated bilirubin (≥ 1.2 mg/dl) ($p < 0.05$) level. However, no hotspot mutation was detected in healthy control.

Conclusions: Non-invasive molecular profiling may be used as prognostic biomarkers and targeted therapies for personalized treatment plan and real-time monitoring of tumor dynamics.

Performance of Circulating 5-Hydroxymethylcytosine Epigenetic Signatures in Detecting Hepatocellular Carcinoma Among Patients with Cirrhosis

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Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer mortality globally, predominantly arising in cirrhotic patients. Current surveillance strategies lack sensitivity for early detection. Circulating cell-free DNA 5-hydroxymethylcytosine (5hmC) signatures represent a promising non-invasive biomarker. We evaluated the diagnostic accuracy of 5hmC-based assays versus alpha-fetoprotein (AFP) for HCC detection in cirrhotic populations.

Methods: We performed a bivariate random-effects meta-analysis using the Reitsma model to synthesize sensitivity and specificity across diagnostic studies. Studies evaluating 5hmC as an HCC biomarker in cirrhotic patients were included, with head-to-head AFP comparisons analyzed separately. Key metrics included pooled sensitivity, specificity, and SROC area under the curve (AUC).

Results: Four studies were included for 5hmC analysis, with three providing direct AFP comparisons. 5hmC demonstrated a pooled sensitivity of 68.2 percent (95 percent CI: 40.5-87.1 percent) and a false positive rate of 14.8 percent (95 percent CI: 5.4-34.5 percent), yielding an SROC AUC of 0.846. AFP showed variable performance with a mean AUC of 0.754 (range: 0.692-0.845). In head-to-head comparisons, 5hmC consistently outperformed AFP across all three studies, with a mean absolute AUC improvement of 9.03 percent. Considerable between-study heterogeneity was observed ($I^2 = 72$ percent), and leave-one-out sensitivity analysis indicated that pooled estimates were influenced by individual study inclusion.

Conclusion: 5hmC signatures appear to provide higher diagnostic accuracy than AFP for detecting HCC in cirrhotic patients. However, significant heterogeneity and the limited number of studies suggest that large-scale prospective validation is necessary before incorporating this into clinical surveillance protocols.

Identification of Novel Prognostic Biomarkers and Molecular Pathogenesis Insights in Hepatocellular Carcinoma through Integrated Multi-Database Analysis

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Objective: This study aimed to discover novel prognostic biomarkers and unravel molecular pathogenesis in hepatocellular carcinoma (HCC) through an integrative analysis of transcriptomic, proteomic, and clinical data from GEPIA, TCGAexplorer, OMIM, and UALCAN databases.

Methods: We applied a multi-layered bioinformatics pipeline combining differential gene expression analysis from GEPIA with survival and clinical correlates from TCGAexplorer. Functional relevance was established via OMIM annotations, while UALCAN validated protein expression patterns in tumor progression. Additionally, pathway enrichment and molecular network reconstruction enabled delineation of key oncogenic processes.

Results: Our analysis identified CDC20, CLEC1B, CYP2C9, and LCAT as novel prognostic biomarkers exhibiting significant overexpression in HCC tissues and strong correlation with inferior overall survival. OMIM and pathway analyses linked these genes to cellular proliferation, immune regulation, and metabolic reprogramming critical in HCC progression. Importantly, UALCAN-based protein validation demonstrated elevated expression in advanced-stage tumors and high-grade malignancies. Integrative pathway mapping highlighted dysregulation of cell cycle checkpoints, PI3K/AKT signaling, and immune evasion pathways involving these biomarkers.

Conclusion: This study leverages a novel integrative multi-omics framework to identify and validate clinically relevant biomarkers, advancing precision oncology for HCC. The identified gene panel offers potential for improved prognostic stratification and therapeutic targeting, illuminating molecular mechanisms underlying liver cancer aggressiveness.

BEP3-4 10222

The VETC Associated Trabecular Subtypes in Non-cirrhotic HCC is Defined by Loss of Tumor Suppressor and Downregulation of Ribosomal Genes

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Background: Vessels Encapsulating Tumor Clusters (VETC) represent a distinct angiogenic pattern associated with metastasis in hepatocellular carcinoma (HCC). This study aimed to characterize VETC-associated trabecular subtypes and their genetic and transcriptomic profiles in non-cirrhotic HCC (NCHCC).

Methods: Fifty-three NCHCC specimens were analyzed using CD34 immunohistochemistry to classify tumors as VETC positive or VETC negative. Histologic patterns were correlated with molecular markers including p53, beta-catenin, EpCAM, and CD8 positive T cells. Genomic profiling was performed using targeted next-generation sequencing (n=11) and RNA sequencing (VETC positive n=7; VETC negative n=3).

Results: VETC positive tumors were identified in 20.75 percent of cases and predominantly displayed microtrabecular (55 percent) and macrotrabecular (45 percent) growth patterns. They were associated with younger age (mean 55.7 years), tumor size greater than 10 cm (90 percent), elevated alpha-fetoprotein levels (64 percent), and universal EpCAM expression (P=0.027). Clinically, VETC positive cases showed high recurrence (64 percent) and poor overall survival, with survival less than 2 years in 64 percent of patients (P<0.01). This phenotype demonstrated an immune-excluded microenvironment with reduced CD8 positive T cell infiltration (P=0.041) and frequent TP53 and RB1 mutations (approximately 60 percent). Transcriptomic analysis revealed downregulation of ribosomal biogenesis (RPL34), protein processing (CLU), and metabolic pathway genes (APOA2, ADH1B).

Conclusion: VETC positivity identifies a highly aggressive NCHCC subtype associated with adverse clinical outcomes. This phenotype is marked by transcriptional repression of ribosomal biogenesis, metabolic reprogramming, and an immune-excluded tumor microenvironment, supporting its relevance for risk stratification and personalized therapeutic strategies.

Hepatocellular Carcinoma in Armenia: Primary Assessment of Molecular Alterations

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Background: Hepatitis B virus (HBV) genotypes exhibit distinct biological and epidemiological characteristics. The aim of the study was to understand the distribution of HBV genotypes and the profile of cancer mutations among patients with liver cirrhosis (LC) and hepatocellular carcinoma (HCC) in Armenia.

Methods: We used droplet digital polymerase chain reaction (ddPCR) to identify the presence of occult HBV infection in the plasma of patients, as well as to determine the viral subtype. The study included 91 cases of liver cirrhosis and 69 cases of hepatocellular carcinoma.

Results: Our study revealed that 18.8% of HCC patients were HBV positive (in contrast to 4.4% in LC patients). Furthermore, 46.6% of HCC patients were documented to have an occult HBV infection, as opposed to 24.1% of LC patients. The majority of HBV cases constituted the D genotype. Our results revealed a high frequency of TERT promoter mutations in HCC cases (24%), along with AFB1-associated TP53 mutations (3%) detected in free-circulating DNA (fcDNA). In comparison, mutations were significantly less common in liver cirrhosis patients (3% and 7%, respectively, $P=0.0057$). Additionally, the mutation burden (mutated copies/mL) was significantly higher in HCC patients than in those with LC ($P=0.0063$).

Conclusion: HBV subtype variants correspond to the overall distribution of genotypes in this part of Eurasia, while occult HBV infections were highly prevalent. Circulating plasma mutations represent promising tools for diagnosis and monitoring of treatment. Further genomic characterization may help establish relationships between alteration frequency and HCC-related mortality.

Global Research Landscape and Thematic Evolution of Immune Cell Metabolic Reprogramming in Liver Disease and Hepatic Oncology: A Bibliometric and Science Mapping Analysis

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Background: Immune cell metabolic reprogramming plays a pivotal role in regulating immune activation, differentiation, and effector function. Metabolic remodeling of the hepatic microenvironment critically shapes immune tolerance, inflammation, and tumor immune escape.

Methods: A bibliometric and science mapping analysis was performed using publications indexed in the Web of Science Core Collection from 2008. A total of 5747 articles and reviews were included. VOSviewer and CiteSpace were applied to analyze publication trends, collaboration networks, keyword co-occurrence, reference co-citation, thematic timelines, and citation burst patterns, with emphasis on liver disease and hepatic oncology related research clusters.

Results: Research output followed a canonical life-cycle trajectory, comprising an initial foundational phase (2011-2014), a period of rapid expansion and conceptual consolidation (2015-2018), and volume-driven growth with partial decoupling between publication output and citation impact after 2022. China and the United States were the most productive contributors, while the United States and several European countries demonstrated higher citation impact and network centrality. Keyword co-occurrence and reference co-citation analyses identified three major pillars: metabolic reprogramming of innate immune cells and trained immunity in chronic liver inflammation; tumor microenvironment driven immunometabolic regulation in hepatocellular carcinoma, including hypoxia, nutrient competition, and metabolite accumulation; and metabolic checkpoints governing adaptive immune dysfunction and exhaustion in liver tumors. Emerging themes highlight a shift toward metabolite mediated signaling and epigenetic regulation, including lactylation and metabolite driven chromatin remodeling.

Conclusions: Immune cell metabolic reprogramming represents a mature yet rapidly diversifying research field with increasing relevance to liver disease and hepatic oncology.

BEP4-2 10066

The Relationship between the Expression of Tumor Microenvironment-related Genes and the Gene Mutations of Hepatocellular Carcinoma from TCGA Data

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Background: In the treatment of advanced hepatocellular carcinoma, systemic therapies target the tumor microenvironment. The Cancer Genome Atlas (TCGA) includes not only gene mutation but also comprehensive gene expression. By using genes specifically expressed in microenvironmental cells, it is possible to evaluate the relationship between the state of the tumor microenvironment and the gene mutations.

Methods: Gene mutation and expression data from 360 pre-processed hepatocellular carcinoma cases were downloaded from the GDAC Firehose browser and analyzed using the statistical software R. The correlation and network analysis of 20,500 gene expressions were performed to identify gene sets expressed in immune cells, fibroblasts (FB), and vascular endothelial cells (VE). Principal component analysis (PCA) was conducted for each gene set, and the effects of 14,882 gene mutations on the first principal component were examined using t-tests.

Results: Pearson correlation analysis identified 541 genes with a correlation coefficient of 0.9 or higher. Among these, 127 immune cell markers including CD8, 23 FB markers including COL1A1, and 8 VE markers including TIE1 were extracted. PCA for each gene set revealed that the gene mutation most strongly associated with the first principal component was TTN mutation in the immune cell group ($p=0.00013$), CTNNB1 mutation in the FB marker group ($p<10^{-9}$), and TP53 mutation in the VE marker group ($p<10^{-7}$). CTNNB1-mutated cases showed decreased expression of FB markers, and TP53-mutated cases showed decreased expression of VE markers.

Conclusion: The study examined the relationship between tumor microenvironment-related gene expression and the specific gene mutations in hepatocellular carcinoma.

Integrative Machine Learning and Experimental Validation Identify MYBL2 as a Prognostic Biomarker and Therapeutic Target in Hepatocellular Carcinoma

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Background: Hepatocellular carcinoma (HCC) presents poor treatment outcomes. The MYB family of oncogenes is implicated in cancer, but its clinical utility in HCC remains underexplored.

Methods: We applied an integrative pipeline combining LASSO based feature selection on TCGA and GEO cohorts, single cell transcriptomics, pharmacogenomic surveys, and CRISPR dependency screens, alongside in vitro HepG2 assays, luciferase reporter tests, iTRAQ proteomics, and an in vivo western diet/CC14 HCC model using miR 29a transgenic mice.

Results: MYBL2 robustly discriminated tumor from normal liver (AUC = 0.968) and high expression was associated with adverse features, including higher grade, microvascular invasion, HBV positivity, no response to TACE, and worse survival. A nomogram combining MYBL2 with AJCC stage improved 1, 3, and 5 years AUCs versus stage alone. MYBL2 correlated with AFP, MKI67, PCNA, and BIRC5; Single cell analyses linked MYBL2 to cell cycle programs and reduced inflammatory signatures. CRISPR screens showed growth inhibition in most HCC lines after MYBL2 knockout. Pharmacogenomic analyses associated high MYBL2 with greater sorafenib sensitivity. Bulk and single cell data connected MYBL2 to an immunosuppressive microenvironment and higher MSI, with reduced MYBL2 in tumor plasmacytoid dendritic cells. Mechanistically, miR 29a directly suppressed MYBL2 translation; miR 29a transgenic mice were protected from WD/CC14 induced HCC, and iTRAQ proteomics identified MYBL2 among the top miR 29a regulated proteins.

Conclusions: MYBL2 is a potent diagnostic and prognostic biomarker in HCC, predicting sorafenib sensitivity, and is a tractable target of miR 29a based suppression, warranting clinical validation for patient stratification and therapeutic development.

BEP4-4 10203

Clinical Significance of Serum VEGF Levels in Patients with Unresectable Hepatocellular Carcinoma Treated with Durvalumab plus Tremelimumab

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Background: Establishing biomarkers to optimize treatment selection for unresectable hepatocellular carcinoma (HCC) remains an unmet medical need. Although serum VEGF is associated with angiogenesis and prognosis in HCC, its dynamics during immunotherapy are not well understood. This study evaluated the clinical significance of serum VEGF in patients treated with durvalumab plus tremelimumab (D+T).

Methods: We analyzed 31 patients with unresectable HCC receiving D+T. Serum VEGF levels were measured at baseline and 4 weeks post-treatment. Tumor response was assessed via RECIST v1.1.

Results: Median age was 74 years; 25 patients (80%) were male. Treatment lines were 1st/2nd/3rd or later in 6/11/14 cases, respectively. Median baseline VEGF was 231 pg/ml. The high-baseline VEGF group (>231 pg/ml) showed a trend toward longer median survival compared to the low group (16.3 vs. 8.7 months, $p=0.12$), though progression-free survival (PFS) did not differ significantly (2.0 vs. 2.7 months, $p=0.91$). While high-baseline VEGF correlated with higher AFP and PIVKA-II, these differences were not significant. In 20 patients with serial data, VEGF increased from a median of 290 to 397 pg/ml at 4 weeks ($p=0.05$). Notably, no objective responses were observed in patients whose VEGF increased by >50%. There was no significant difference in PFS regarding VEGF elevation.

Conclusion: Baseline serum VEGF was not a predictive factor for prognosis or PFS in D+T therapy. However, a marked post-treatment increase in VEGF may be associated with a lack of clinical response.

Impact of Hepatocyte Nuclear Factor-1 Alpha Genetic Variants on Hepatocellular Carcinoma Susceptibility among Patients with and without Diabetes Mellitus

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Background: Variants of the hepatocyte nuclear factor 1 alpha (HNF1A) gene have been implicated in the pathogenesis of maturity-onset diabetes mellitus (DM). Diabetes mellitus is a well-established risk factor for hepatocellular carcinoma (HCC); however, the association between HNF1A genetic variants, DM, and subsequent HCC development in cirrhotic patients remains unclear. We aimed to assess whether HNF1A genetic variants act as cofactors with diabetes mellitus in promoting HCC development among hepatitis C virus (HCV) infected patients.

Methods: A total of 140 participants were enrolled and categorized into three patient groups: 30 HCC without DM, 30 HCC and DM, and 40 DM without HCV infection or HCC. 80 age- and sex-matched healthy individuals served as controls. All participants underwent liver function testing, assessment of hepatitis viral markers, alpha-fetoprotein (AFP) measurement, fasting blood glucose, HbA1c evaluation, and genotyping of HNF1A polymorphisms (rs2464196 and rs1169310) using real-time PCR.

Results: The HNF1A rs2464196 AA genotype was significantly more frequent in patients with DM, HCC, and combined HCC with DM compared with controls. Similarly, the dominant model (AA + GA) was significantly more prevalent in all patient groups than the GG genotype. Notably, the AA genotype was most common among patients with both HCC and DM. In contrast, no significant differences were observed in genotype or allele frequencies of HNF1A rs1169310 across the studied groups.

Conclusion: The findings suggest that the HNF1A rs2464196 AA genotype may be associated with diabetes mellitus and could increase susceptibility to HCC in HCV-infected patients. Conversely, rs1169310 showed no significant association.

Risk Factors for Hepatocellular Carcinoma Development after Direct-acting Antiviral Therapy in Hepatitis C: A Long-term Follow-up Study

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Introduction: Direct-acting antivirals (DAAs) have dramatically improved treatment outcomes for chronic hepatitis C virus (HCV) infection, achieving high sustained virological response (SVR) rates. Nevertheless, the risk of hepatocellular carcinoma (HCC) persists after viral eradication, particularly in patients with advanced liver fibrosis. This study aimed to identify risk factors for HCC development after DAA therapy, with a particular focus on liver stiffness measurement (LSM).

Methods and Results: We retrospectively analyzed 597 HCV-infected patients who received DAA therapy between January 2013 and December 2023. Patients with a prior history of HCC or unsuccessful LSM were excluded from the HCC risk analysis. Cumulative HCC incidence increased proportionally with higher LSM values ($P < 0.001$). The overall 5-year and 10-year cumulative incidences of HCC were 6.5% and 15.0%, respectively. The annual incidence rate was 0.5% per person-year in patients with LSM < 10 kPa, compared with 5.8% per person-year in those with LSM ≥ 20 kPa. Multivariate analysis identified advanced fibrosis (LSM ≥ 20 kPa; HR = 17.0, 95% CI 5.86-49.4), older age (HR = 1.076, 95% CI 1.02-1.13), and elevated γ -GTP (HR = 1.008, 95% CI 1.00-1.01) as independent risk factors for HCC after SVR.

Conclusion: Although DAA therapy achieves viral eradication, advanced liver fibrosis (LSM ≥ 20 kPa) remains the strongest residual risk factor for HCC after SVR. Therefore, patients with advanced fibrosis require continued surveillance and timely diagnosis, enabling early therapeutic intervention and improved clinical outcomes.

HCC Development in HCV-Infected Patients after Virological Response

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Background: Despite high cure rates of HCV-infection treatment with direct-acting antiviral drugs (DAAs) and as a consequence reduced incidence of hepatocellular carcinoma (HCC), risk of liver primary cancer still exists even after sustained virological response (SVR). Older age, diabetes, hepatitis, alcohol use and lack of fibrosis reversal are increased HCC risk after HCV cure.

Methods: 78 HCV-infected patients with F3 (27%) and F4 (73%) from 33 to 73 years old (70% male, 55.8 \pm 9.1years old, BMI 27.1 \pm 5.0kg/m², treated with DAA-contain regimens involved in the study. AFP checked in all patients (normal < 8.78 ng/mL). PIVKA-II checked in patients with elevated AFP or liver nodules on US. Serum levels of PIVKA-II were measured using the chemiluminescent assay of the Architect 1000i System, Abbott with cut of < 50.9 mAU/mL.

Results: AFP range 1.4-135.3ng/mL, average 13.5 \pm 2.6(m \pm SE) was elevated in 35% of patients. Despite SVR HCC suspected in 8 patients with F4(87.5% male) rely on Imaging, dynamics of AFP and PIVKA-II. 5 of them with HCC staging was C or B despite awareness not pass regular US control every 6 months. Interestingly HCC developed from 2 up to 8 years from achieving SVR. Data concerning HCC suspected patients in Tab1. 10 patients with decompensated cirrhosis died despite SVR (12.8%), among them 3 with HCC.

Conclusions: Risk of HCC development in patients with HCV-associated cirrhosis required close monitoring by US and AFP checking every 6 months after SVR. Serum levels of PIVKA-II in combination with AFP and imaging technics can help in early diagnosis of HCC.

Early Detection of De Novo Hepatocellular Carcinoma by AFP-L3 Fraction Following SVR for HCV: A Case Report

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Background: Hepatocellular carcinoma (HCC) is typically diagnosed using contrast-enhanced CT or MRI, with gadoteric acid-enhanced MRI (EOB-MRI) offering high sensitivity. However, conventional tumor markers often lack sensitivity in early-stage HCC, limiting their utility in surveillance. We report a case in which an elevated AFP-L3 fraction preceded radiological detection of de novo HCC after sustained virological response (SVR) to hepatitis C virus (HCV) therapy.

Case Summary: A 74-year-old man achieved SVR in 2015 with sofosbuvir plus ledipasvir. In October 2021, he was referred for elevated AFP-L3 fraction. Laboratory findings revealed AFP 12.2 ng/mL, AFP-L3 fraction 57.1%, and PIVKA2 25 mAU/mL. EOB-MRI at that time showed no evidence of HCC. Four months later, in February 2022, repeat EOB-MRI identified a 1.1 cm lesion in segment 3, exhibiting arterial phase hyperenhancement and hepatobiliary phase hypointensity, consistent with HCC. The patient underwent hepatic resection in April 2022. Postoperatively, tumor markers normalized, and he remains recurrence-free.

Discussion: AFP, AFP-L3 fraction, and PIVKA2 are widely used as independent biomarkers for HCC. Among them, AFP-L3 fraction is considered more specific. In this case, AFP-L3 elevation prompted early re-imaging, leading to timely diagnosis and curative resection. This underscores the potential role of AFP-L3 in surveillance, particularly when imaging is initially negative.

Conclusion: AFP-L3 fraction positivity may serve as an early indicator of occult HCC, even in the absence of radiological findings. Timely follow-up imaging in such cases can facilitate early diagnosis and improve clinical outcomes.

HCP1-4 10081

A Case of Hepatocellular Carcinoma with Decompensated Hepatitis C-related Liver Cirrhosis that Achieved a Sustained Virological Response after Retreatment with Glecaprevir/Pibrentasvir

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There is no established strategy for direct-acting antiviral (DAA) retreatment in patients with decompensated liver cirrhosis (LC) who experience DAA failure. We report a case of a patient with decompensated hepatitis C-related LC complicated by hepatocellular carcinoma (HCC) who failed sofosbuvir/velpatasvir (SOF-VEL) therapy but subsequently achieved a sustained virological response (SVR) after retreatment with glecaprevir/pibrentasvir (GLE/PIB), with approval from our ethics committee. A woman in her 70s presented after abnormal liver function was detected during a health check. She had been HCV antibody-positive for more than 10 years without prior treatment and was infected with HCV genotype 1b, with an HCV RNA level of 7.1 log IU/mL. Pretreatment screening revealed HCC, and gadoteric acid-enhanced magnetic resonance imaging demonstrated multiple tumors measuring up to 21 mm in diameter. Serum AFP was 61.6ng/mL and PIVKA-II was 18mAU/mL, respectively. Liver function was classified as Child-Pugh score (CPS) 7, an ALBI score of -1.99, and mALBI grade 2b. Lenvatinib plus transcatheter arterial embolization was initiated, followed by radiofrequency ablation after worsening ascites, achieving radiological response. She subsequently received 12 weeks of SOF/VEL therapy for decompensated LC but did not achieve SVR. Resistance testing revealed L31I/M and Y93H mutations without a P32 deletion. Seven months later, after improvement of liver function to CPS 5 and confirmation of no HCC recurrence, she underwent 12 weeks of GLE/PIB therapy and successfully achieved SVR. This case suggests that carefully selected retreatment strategies may be feasible in patients with decompensated LC who fail SOF/VEL therapy.

Ruptured Hepatocellular Carcinoma in an Untreated HCV Patient: Emergency Management, Viral Eradication, and Aggressive Recurrence

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Background: Despite the widespread use of direct acting antivirals (DAAs), untreated hepatitis C virus (HCV) patients remain at risk for hepatocellular carcinoma (HCC). HCC rupture is not rare and life threatening. This case report highlights successful emergency intervention, subsequent viral eradication, and unexpected aggressive recurrence.

Case Presentation: A 67 year old male with no prior antiviral therapy presented in June 2023 with ruptured HCC. Emergency transcatheter arterial embolization (TAE) was performed, followed by curative hepatic resection. In January 2024, DAA therapy was initiated, achieving sustained virological response (SVR). Despite viral eradication, in October 2025 the patient developed recurrent HCC with portal vein tumor invasion. He is currently receiving atezolizumab plus bevacizumab combination therapy.

Discussion: This case is notable for several reasons. First, HCC rupture served as the initial manifestation in an untreated HCV patient, necessitating immediate life saving intervention. Second, curative resection and subsequent DAA therapy successfully achieved SVR, eliminating viral replication. However, recurrence with portal vein invasion occurred within two years, underscoring that SVR does not abolish the risk of aggressive HCC relapse. The case emphasizes the ongoing presence of untreated HCV patients in Japan and elsewhere, and the need for vigilance even after viral eradication. Continuous surveillance remains essential, particularly in patients with advanced disease.

Conclusion: Untreated HCV patients may present with catastrophic HCC rupture. Emergency management and viral eradication can prolong survival, but recurrence risk persists, highlighting the importance of lifelong follow up.

Hepatocellular Carcinoma in Japanese Autoimmune Hepatitis: Management and Outcomes

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Background: Hepatocellular carcinoma (HCC) in autoimmune hepatitis (AIH) was considered rare but is increasing with prolonged prognosis. Its impact on the overall prognosis of AIH is unknown, and treatment has not been established.

Aim: To investigate the risk factors and prognosis of HCC in patients with AIH and identify appropriate management strategies.

Methods: We studied patients with AIH including background liver disease, sex, age, complications, treatment, response to treatment, liver fibrosis, prognosis, and treatment.

Results: In 131 patients, deaths due to liver failure were more common early after the onset of AIH; however, deaths due to HCC increased gradually. HCC was observed in 12 patients (median age, 70 years; male/female, 4/8; cirrhosis at onset, 11; median time to carcinogenesis, 7 years). Cirrhosis at diagnosis was identified as a risk factor for carcinogenesis in the multivariate analysis (odds ratio, 41.36; $p < 0.0001$) and cumulative cancer rates were high. Multidisciplinary therapy other than immune checkpoint inhibitors was administered as treatment for HCC. Two of the three patients who used molecular-targeted drugs discontinued the treatment because of adverse events.

Conclusion: HCC is an important cause of death in patients with AIH. Currently available drug therapies are limited and early detection is desirable.

A Study on Hepatocellular Carcinoma with Autoimmune Hepatitis as Background Liver Disease

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Background: To examine the clinical characteristics of hepatocellular carcinoma (HCC) in patients with autoimmune hepatitis (AIH) as the underlying liver disease.

Methods Subjects and Methods: We retrospectively reviewed cases of radiofrequency ablation (RFA) performed for primary HCC between January 2008 and October 2025, focusing on those with AIH as the underlying liver disease. We examined age, sex, reserve capacity of the underlying liver, tumor status, and steroid administration status.

Results: During the study period, 1,456 RFA procedures were performed. After excluding metastatic liver cancer and HCC originating from other primary cancers (e.g., intrahepatic cholangiocarcinoma), 229 cases underwent treatment for primary HCC. Among these, 7 cases had AIH as the underlying liver disease. There were 3 males and 4 females, with a median age of 78 years (range 67-85 years). The median maximum tumor diameter was 25 mm (range 17-57 mm), and the number of treated lesions ranged from 1 to 4. The Child-Pugh score was 5 (range 5-9), with 4 cases classified as Child A and 3 as Child B. The median follow-up period was 58.9 months (range 15.1-132.9 months). Among the 6 patients whose survival status was known, 5 had expired. Steroid administration at the time of tumor development was not performed in 5 of the 7 cases.

Conclusion: Among the cases treated with RFA for primary HCC at our institution, 3.1% had AIH as a background liver disease. Tumor size, hepatic reserve capacity, and prognosis varied.

Late-Onset Hepatic Failure (LOHF) Caused by Seronegative Acute-Onset Autoimmune Hepatitis Requiring Liver Transplantation

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A woman in her 50s with no comorbidities had intermittently been noted to have mild liver dysfunction since early adulthood, which resolved spontaneously without evaluation. On day 0, she developed dizziness, fatigue, and intermittent acholic stools, followed by progressive liver dysfunction detected in next month. She had no history of alcohol consumption or regular medications. Serologic testing for viral hepatitis and autoimmune liver disease, including antinuclear and anti-smooth muscle antibodies, was negative, and serum IgG levels were within the normal range. Despite treatment with ursodeoxycholic acid for presumed cryptogenic liver injury, liver function progressively deteriorated. A liver biopsy showed nonspecific inflammatory changes without a definitive diagnosis. Day 91 since onset, she was readmitted with severe coagulopathy and rapidly progressed to hepatic encephalopathy. We diagnosed her with acute liver failure. High-dose methylprednisolone pulse therapy failed to improve liver function. The patient was transferred to our institution with grade II hepatic encephalopathy on day 96, and plasma exchange was initiated. CT scan demonstrated marked hepatic atrophy and heterogeneous parenchymal changes. Based on the clinical course, she was diagnosed with LOHF, and deceased-donor liver transplantation was performed. The postoperative course was uneventful, and liver function recovered. Histopathological examination of the explanted liver revealed widespread hepatocellular degeneration with regenerative nodules, prominent lymphoplasmacytic infiltration, and interface hepatitis, consistent with autoimmune hepatitis. This case highlights acute-onset, seronegative autoimmune hepatitis may progress to LOHF and respond poorly to steroid therapy. Early recognition of this entity and timely referral for liver transplantation are essential for improving outcomes.

HCP2-4 10057

Validation of PBC-10 in Japanese Patients with Primary Biliary Cholangitis

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Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease that has a substantial impact on health-related quality of life (HRQOL). The PBC-10, a shortened HRQOL assessment tool for PBC, was developed for rapid screening in clinical practice. This study aimed to evaluate the reliability and validity of the Japanese version of the PBC-10 in Japanese patients with PBC.

Methods: HRQOL data from 496 Japanese outpatients with PBC, collected between 2015 and 2016, were retrospectively analyzed. Reliability was assessed using Cronbach's alpha, item-total score correlations, and evaluation of ceiling and floor effects. Validity was examined by assessing correlations between PBC-10 scores and the total and subdomain scores of the Japanese version of the PBC-40, a PBC-specific, well-validated HRQOL questionnaire.

Results: The Cronbach's alpha coefficient for the PBC-10 was 0.872, indicating high internal consistency. Strong item-total score correlations were observed for all items. No ceiling effects were identified, whereas floor effects were present for all items. The total PBC-10 score showed a very strong positive correlation with the total PBC-40 score ($\rho = 0.964$, $p < 0.001$). In addition, strong correlations were observed between most PBC-10 items and the PBC-40 subdomains, supporting its validity.

Conclusions: The Japanese version of the PBC-10 is a reliable and valid tool for the rapid assessment of HRQOL in Japanese outpatients with PBC. It may be useful for identifying patients who could benefit from novel therapies aimed at symptom relief.

Changes in Symptomatic Presentation at Diagnosis and Prognostic Impact in Primary Biliary Cholangitis

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Background: Despite advances in medical therapy for primary biliary cholangitis (PBC), some patients still progress to end-stage liver disease requiring transplantation. We investigated temporal trends in symptomatic presentation at diagnosis and their association with prognosis using data from the 17th nationwide PBC survey in Japan.

Methods: A total of 2,051 patients were registered in the 17th nationwide survey (2023-2024). Among them, 1,005 patients with less than 1-year follow-up and complete symptom and outcome information were analyzed. The prevalence and type of symptoms at diagnosis were compared across diagnostic periods. Prognostic factors for liver-related death or liver transplantation were assessed using Cox proportional hazards models.

Results: Of 1,005 patients (80.4% female; mean age 60.9±11.9 years), 18.9% presented with symptoms at diagnosis: pruritus (12.7%), esophagogastric varices (5.1%), jaundice (4.4%), ascites (2.8%), and edema (2.6%). Excluding pruritus, symptomatic cases accounted for 11.3%. The proportion of symptomatic patients showed no decline across diagnostic eras. During a mean follow-up of 5.0±4.1 years, 34 patients developed liver-related death or transplantation. Symptomatic presentation (HR 6.96, 95% CI 1.59-30.5, p=0.010) and lower albumin levels at diagnosis (HR 9.28, 95% CI 1.92-44.6, p=0.006) independently predicted poor outcomes.

Conclusions: Approximately 10% of patients with PBC continue to present with advanced symptoms at diagnosis, with no recent improvement. Early identification before symptomatic onset remains essential to improve long-term outcomes.

Aetiology–Specific Risk of Hepatocellular Carcinoma in Metabolic Dysfunction–Associated Steatotic Liver Disease

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Background: The global burden of hepatocellular carcinoma (HCC) is shaped by heterogeneous underlying liver disease aetiologies. While viral hepatitis and alcohol-related liver disease are well-established drivers of HCC risk, the contribution of metabolic dysfunction-associated steatotic liver disease (MASLD), particularly in the setting of dual aetiologies, remains incompletely defined. As MASLD increasingly coexists with other chronic liver disease aetiologies, understanding whether MASLD confers additional HCC risk is critical for risk stratification and surveillance strategies.

Methods: We analysed longitudinal data from the CORE dataset to evaluate the association between liver disease aetiology and incident HCC. Cox proportional hazards regression with robust standard errors was used to estimate hazard ratios (HRs) for HCC across aetiologic categories.

Results: A total of 41 incident HCC events were recorded. In aetiology-focused analyses, neither MASLD with alcohol co-aetiology nor MASLD with viral hepatitis co-aetiology was associated with an increased risk of HCC compared with the reference aetiology. Specifically, MASLD with alcohol co-aetiology demonstrated no excess risk of HCC (HR=0.93, 95% CI 0.21–4.16, p=0.922), while MASLD with viral hepatitis co-aetiology was similarly not associated with elevated HCC risk (HR=0.86, 95% CI 0.42–1.78, p=0.691).

Conclusion: In this cohort, MASLD alone or in combination with alcohol or viral hepatitis was not associated with an increased risk of HCC after multivariable adjustment. These findings suggest that MASLD and MASLD-related dual aetiologies may not independently confer excess HCC risk beyond established demographic factors, highlighting the importance of refined risk stratification in MASLD populations.

HCP3-2 10087

Characteristics of Hepatocellular Carcinoma Arising from Alcohol-associated Steatotic Liver Disease

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Background: The proportion of hepatocellular carcinoma (HCC) attributable to alcohol-associated liver disease (ALD) has been increasing. Comprehensive characterization of the clinical features of ALD- and MetALD (metabolic dysfunction-associated liver disease and increased alcohol intake)-related HCC is needed. We investigated the clinical characteristics of HCC arising from ALD and MetALD.

Methods: Among 882 patients diagnosed clinicopathologically with alcohol-related steatotic liver disease at our institution from 1980 to 2024, 848 patients without viral hepatitis (including 51 without cardiometabolic risk factors <CMRFs>) were enrolled. The cohort consisted of 633 patients with ALD (including 35 without CMRFs) and 199 with MetALD; HCC was identified in 282 patients (33.3%). We compared clinical features between patients with ALD-HCC (n = 229, 36.2%) and MetALD-HCC (n = 51, 25.6%).

Results: Compared with ALD-HCC, MetALD-HCC patients were significantly older (64 vs. 70 years), more frequently obese (53.3% vs. 66.7%), and less likely to have cirrhosis (81.3% vs. 58.0%). Laboratory findings showed higher serum albumin (3.6 vs. 3.9 g/dL), prothrombin time (78.5% vs. 90.5%), and platelet count (12.1 vs. 15.1 ×10⁴/μL; p = 0.05), and lower total bilirubin (0.9 vs. 0.6 mg/dL) in MetALD-HCC (all p < 0.01 except platelet count). No significant differences were observed in sex distribution or other CMRF prevalence.

Conclusions: Patients with MetALD-HCC were significantly older, and notably, HCC occurred even in non-cirrhotic patients with preserved liver function. Careful surveillance is warranted in this population.

Intermittent Fasting, Liver Fibrosis, and Hepatocellular Carcinoma Risk in Non-Alcoholic Fatty Liver Disease: A Scoping Review

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Non-alcoholic fatty liver disease (NAFLD) is a rapidly growing cause of hepatocellular carcinoma (HCC), frequently developing even in non-cirrhotic livers. Interventions targeting hepatic steatosis, fibrosis, and inflammation may therefore influence HCC risk. Intermittent fasting (IF), including Ramadan fasting and time-restricted feeding (TRF), has emerged as a metabolic intervention with potential hepatoprotective effects, yet its relevance to HCC-related pathways remains unclear. This scoping review was conducted in accordance to the Arksey and O'Malley framework and reported with the PRISMA-SCR guidelines. Observational studies, quasi-experimental studies, and randomized controlled trials evaluating intermittent fasting strategies in adult with NAFLD were included. Data were systematically extracted on study characteristics, fasting modality and duration, and liver-related outcomes. Outcomes of interest included liver enzymes, non-invasive fibrosis indices (FIB-4 and NAFLD Fibrosis Score), and imaging-based parameters such as liver stiffness measurement (LSM) and controlled attenuation parameter (CAP). Evidence was synthesized descriptively. Intermittent fasting was consistently associated with reductions in liver enzyme levels. Several studies reported improvements in non-invasive fibrosis markers and imaging-based outcomes, including reductions in LSM and CAP. Ramadan fasting showed beneficial effects on hepatic steatosis and inflammatory markers, while TRF combined with dietary modification demonstrated greater improvements in fibrosis-related parameters compared with control diets. Intermittent fasting is associated with improvements in steatosis, fibrosis, and inflammation, which are key pathways implicated in NAFLD-related hepatocarcinogenesis. However, evidence is limited by small sample sizes, heterogeneous study designs, short follow-up durations, and the absence of direct oncologic endpoints such as HCC incidence. Further large-scale, long-term prospective studies are warranted.

HCP3-4 10159

Sarcopenia in Cirrhotic Patients: Prevalence, Prognostic Impact, and Clinical Outcomes

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Background and Aims: Sarcopenia is the loss of skeletal muscle mass and function. It is a common complication of liver cirrhosis with poor clinical outcomes. This study aimed to determine sarcopenia prevalence across Child-Pugh classes. It also evaluated the prognostic impact on 24-month mortality and the association with Hepatic Encephalopathy.

Methods: This prospective observational cohort study included 280 cirrhotic patients at Benha Teaching Hospital from January 2023 to 2025. Sarcopenia was defined by low muscle mass using CT-based Skeletal Muscle Index and low function using handgrip strength. Patients were followed for 24 months. Logistic regression models assessed the independent association of sarcopenia with mortality and Hepatic Encephalopathy. The models adjusted for age and Child-Pugh class.

Results: Overall sarcopenia prevalence was 46.8 percent. It increased significantly with disease severity. Prevalence was 22.8 percent in Child-Pugh A and 70.7 percent in Child-Pugh C. Muscle mass and handgrip strength showed a strong correlation. In multivariate analysis sarcopenia was an independent predictor of 24-month mortality with an Odds Ratio of 3.36. It was also strongly associated with the incidence of Hepatic Encephalopathy with an Odds Ratio of 3.45.

Conclusion: Sarcopenia is highly prevalent in cirrhotic patients. It is an independent and powerful predictor of 24-month mortality and Hepatic Encephalopathy. These findings underscore the critical need to incorporate sarcopenia screening into routine clinical practice for risk stratification. This will help guide targeted nutritional and physical interventions.

Acid-Suppressing Therapy and the Risk of Hepatic Encephalopathy in Cirrhosis: A Prospective Cohort Study

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Background: Acid-suppressing agents, including proton pump inhibitors (PPIs) and potassium-competitive acid blockers (P-CABs), are frequently prescribed in patients with chronic liver disease. Although associations with hepatic encephalopathy (HE) or spontaneous bacterial peritonitis (SBP) have been reported, causal inference is limited by indication bias. We evaluated these associations using a large prospective cohort.

Methods: Among 1,206 patients enrolled between February 2020 and March 2022, 373 patients with cirrhosis were analyzed. Patients were classified as PPI/P-CAB users or non-users. The primary endpoint was a composite of HE or SBP, and the secondary endpoint was variceal bleeding. Inverse probability of treatment weighting (IPTW) was performed using the following covariates: ALBI score, history of HE, history of ascites, history of gastroesophageal varices (including prior treatment), lactulose use, and rifaximin use. Covariate balance was assessed using standardized mean differences.

Results: Before adjustment, users had more advanced liver dysfunction. After IPTW, baseline characteristics were well balanced between non-users (n = 163) and users (n = 196). The 1- and 2-year cumulative incidences of HE/SBP were 3.7% and 7.5% in non-users and 4.5% and 10.4% in users, respectively, with no significant difference (HR 1.29; 95% CI 0.59-2.79; p = 0.53). The incidence of variceal bleeding was also comparable between non-users and users (HR 0.66; 95% CI 0.19-1.96; p = 0.40).

Conclusion: After adjustment for liver function and prior decompensation-related factors, PPI/P-CAB use was not independently associated with increased risks of HE, SBP, or variceal bleeding in patients with cirrhosis.

Global Trends in Liver Cancer Attributable to Hepatitis B: Insights from the Global Burden of Disease 2023 Study

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Background: Hepatitis B virus (HBV) related liver disease remains a major contributor to global mortality and is a leading cause of primary liver cancer (PLC). Despite progress in vaccination and antiviral therapy, marked regional disparities persist. This study assessed global trends in the prevalence, incidence, and disability adjusted life years (DALYs) of liver cancer attributable to HBV from 2000 to 2023.

Methods: Data were extracted from the Global Health Data Exchange (GHDx) using the Global Burden of Disease (GBD) 2023 dataset on liver cancer attributable to hepatitis B. Global and regional estimates of prevalence, incidence, and DALYs were reported as absolute numbers and age-standardized rates per 100,000 population with 95% uncertainty intervals.

Results: Between 2000 and 2023, the global burden of HBV-related liver cancer declined steadily. The age standardized prevalence rate decreased from approximately 15 per 100,000 population in 2000 to 11 per 100,000 in 2023, representing a reduction of nearly 25%. The decline accelerated after 2010, paralleling the expansion of HBV vaccination programs, wider access to antiviral treatment, and improved surveillance. Nevertheless, the burden remains disproportionately high in East and Southeast Asia, where HBV is historically endemic. Comparable downward trends were observed for incidence and DALYs, reflecting overall improvements in disease control and outcomes.

Conclusion: Although the global burden of HBV related liver cancer has declined substantially, it remains a significant public health challenge in high endemic and low-resource regions. Sustained vaccination efforts, expanded antiviral treatment, and strengthened surveillance are essential to achieve the WHO 2030 hepatitis elimination targets.

HCP4-2 10125

Global Prevalence and Incidence of Primary Sclerosing Cholangitis: An Updated Meta-Analysis

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Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver condition, and a well-established risk factor for cholangiocarcinoma, conferring one of the highest malignancy risks among hepatobiliary disorders. PSC-associated cholangiocarcinoma carries significant morbidity and mortality, yet global prevalence and incidence estimates are highly heterogenous across populations. This meta-analysis evaluates the prevalence and incidence of PSC in the general and inflammatory bowel disease (IBD) populations to inform cholangiocarcinoma risk and surveillance strategies.

Methods: A systematic search of Medline and Embase from inception to October 20, 2025 identified studies reporting on prevalence and incidence rates in the general and/or IBD population. Eligible studies were independently screened, with seventy-five studies meeting inclusion criteria. Pooled prevalence and incidence estimates were calculated using meta-analysis.

Results: Seventeen studies including 196,635,709 individuals showed pooled global prevalence of PSC of 8.06 per 100,000 (95% CI 4.75 - 13.36) in the general population. Among 517,433 patients with IBD in thirty-five studies, pooled PSC prevalence was 15.6 per 1,000 (95% CI 11.0 - 22.0), with a pooled prevalence of 21.1 per 1,000 in ulcerative colitis and 10.3 per 1,000 in Crohn's Disease. Thirteen studies reported a pooled incidence of PSC of 0.892 per 100,000 person-years (95% CI 0.705 - 1.130).

Conclusion: Prevalence of PSC varies among different populations and IBD subtypes, influencing the global burden of PSC-associated cholangiocarcinoma. Robust epidemiological estimates across population subgroups are essential for identification of high-risk individuals to guide surveillance strategies for cholangiocarcinoma and future oncologic studies on risk stratification and early detection.

Genome-wide Association Study of TG/HDL Ratio in 424,865 UK Biobank Participants

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Background: The TG/HDL ratio is an established marker of insulin resistance and cardiovascular risk. We aim to identify SNPs, genes, and biological pathways associated with this ratio to better understand its genetic architecture and potential links to long term outcomes including HCC risk.

Methods: We conducted a genome-wide association study (GWAS) of the TG/HDL ratio in 424,865 participants from the UK Biobank. Quality control was performed using missingness and Hardy-Weinberg equilibrium filters, and linkage disequilibrium was accounted for. Gene-level analyses were subsequently performed using MAGMA to map associated variants to genes and identify enriched biological pathways through gene-set enrichment analysis.

Results: MAGMA gene-set enrichment analysis revealed significant enrichment of pathways associated with hepatocellular carcinoma (HCC). Specifically, gene sets associated with HCC recurrence were enriched among TG/HDL-associated variants ($p=0.0017$, $NES=0.39$), suggesting shared genetic factors between elevated TG/HDL ratio and tumor recurrence mechanisms. Additionally, genes associated with the DNAJB1-PRKACA fusion, a driver mutation characteristic of fibrolamellar HCC, were also enriched ($p=0.0067$, $NES=0.81$), indicating potential overlap with oncogenic pathways.

Conclusions: Genetic variants influencing the TG/HDL ratio are enriched in pathways implicated in HCC development and recurrence. These findings suggest a shared genetic basis between dyslipidemia characterized by elevated TG/HDL ratio and HCC susceptibility.

HCP4-4 10208

Treatment Outcomes of Triple Therapy for 816 NAFLD Patients in Mongolia

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Liver steatosis is highly prevalent in Mongolia. Triple therapy combining statins, Vitamin E, and UDCA has been used as an effective treatment regimen. This prospective and retrospective study analyzed treatment outcomes among 816 patients with liver steatosis who received triple therapy, based on data through years 2023 and 2025 from medical records from Happy-Veritas Hospital. Data were processed using Python's pandas library, with percentages and counts calculated for key variables including steatosis reduction, viral load changes, cirrhosis improvement, and hepatitis virus types. Results demonstrated steatosis reduction in 98.6% of patients, confirming high treatment efficacy for hepatic fat content. Reduction levels were relatively evenly distributed, with the largest proportion of patients showing decreases in the 40 to 99 points on elastography CAP point range within 1 month. The most impressive degree of improvement was from grade 3 to grade 1 steatosis (126 cases). Liver stiffness improved in 77.1% of treated patients. These findings indicate that triple therapy is highly effective in reducing liver steatosis in the Mongolian population, although viral clearance and cirrhosis resolution rates were more moderate. The study provides important baseline data for evaluating triple therapy in Mongolia and underscores the need for larger-scale prospective studies, enhanced prevention strategies, and earlier diagnosis to further improve long-term outcomes.

Hepatoprotective Drugs for the Prevention of Liver Injury among Patients at Risk for Drug-Induced Liver Injury or Chemotherapy-Induced Transaminitis: A Systematic Review and Meta- Analysis

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Background: Drug-induced liver injury (DILI) and chemotherapy-induced transaminitis are important clinical concerns, commonly manifested by elevated transaminases (ALT, AST) and hepatic dysfunction. Several agents, including silymarin, N-acetylcysteine (NAC), and ursodeoxycholic acid (UDCA), are frequently used for hepatoprotection, although evidence supporting their effectiveness in non-tuberculosis settings remains inconsistent. Objective: To assess the effectiveness and safety of silymarin, NAC, and UDCA in preventing liver injury among patients receiving hepatotoxic pharmacologic therapies, particularly chemotherapy and other non-tuberculosis treatments.

Methods: A systematic search of PubMed, Cochrane CENTRAL, ClinicalTrials.gov, and Google Scholar was performed. Randomized controlled trials comparing hepatoprotective agents with placebo or open comparators were included. Primary outcomes were changes in AST and ALT levels and incidence of hepatotoxic adverse events. Risk of bias was evaluated using RoB 2, and certainty of evidence was assessed using GRADE. Meta-analyses were conducted using Review Manager 5.4.

Results: Eight randomized controlled trials involving 325 participants were included. Meta-analysis demonstrated no statistically significant effects on AST (SMD 0.37; 95% CI -0.13 to 0.86) or ALT (SMD 0.21; 95% CI -0.26 to 0.69). No significant reduction in adverse events was observed (RR 0.76; 95% CI 0.37 to 1.56). Substantial heterogeneity was present ($I^2 >75%$), and overall certainty of evidence was very low due to risk of bias, imprecision, and suspected publication bias.

Conclusions: Current evidence does not demonstrate consistent hepatoprotective benefits of silymarin, NAC, or UDCA in patients receiving chemotherapy or other non-tuberculosis hepatotoxic drugs. These agents appear safe but provide uncertain clinical benefit in the studied populations overall.

Five-year Active Surveillance of Unresectable Hepatic Epithelioid Hemangioendothelioma Diagnosed by Repeat Liver Biopsy

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Case: An 80-year-old man presented in January of year X with gross hematuria. Abdominal computed tomography (CT) incidentally revealed multiple hepatic tumors, while no abnormalities were detected in the urinary tract. He was referred to our department for further evaluation. Laboratory tests, including liver enzymes and tumor markers, were within normal limits. Abdominal ultrasonography demonstrated multiple irregular hypoechoic hepatic lesions. Dynamic contrast-enhanced CT revealed bilobar hypovascular tumors, and FDG PET showed abnormal uptake in segments 7 and 2, without evidence of extrahepatic disease. Upper and lower gastrointestinal endoscopy revealed no evidence of a gastrointestinal primary malignancy. Percutaneous liver biopsy was initially inconclusive. A repeat biopsy demonstrated short spindle-shaped atypical cells with fibrous stroma replacing the hepatic sinusoids. Immunohistochemical analysis showed positivity for CD31, CD34, and ERG, leading to a diagnosis of hepatic epithelioid hemangioendothelioma (EHE). Surgical resection was considered but deemed infeasible because of bilobar distribution and proximity to major vascular structures. The patient was therefore managed with active surveillance. After five years, mild progression of intrahepatic lesions with right lobe atrophy was observed; however, liver function remained preserved and the patient remained asymptomatic.

Discussion: EHE is a rare vascular tumor defined by WWTR1-CAMTA1 or YAP1-TFE3 gene fusions, with no established systemic therapy; hepatic EHE shows poor prognosis with extrahepatic disease but may follow an indolent course without it.

Conclusion: This case demonstrates long-term disease control of unresectable hepatic EHE without extrahepatic involvement under active surveillance.

Efficacy of a Novel Ultra Slim Therapeutic Upper Gastrointestinal Endoscope for Pediatric Esophageal Varices A Case Report

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Background: Endoscopic treatment is essential for managing esophageal varices caused by portal hypertension. However, particularly in pediatric and postoperative patients, standard therapeutic endoscopes do not often work because of anatomical narrow lumen. A newly developed slim therapeutic endoscope (EG-840TP; Fujifilm Medical Co., Ltd.), commercialized in March 2023, may be an alternative.

Case Presentation: A 5 month old female infant with congenital biliary atresia who had undergone Kasai portoenterostomy was admitted to our emergency unit because of massive melena. Upper gastrointestinal endoscopy under general anesthesia using an ultra slim endoscope revealed ruptured esophageal varices. Endoscopic hemostasis was attempted; however, neither a standard therapeutic endoscope nor an endoscopic variceal ligation device could be advanced through the pharynx. Because the EG-840TP could be passed, endoscopic injection sclerotherapy (EIS) with aethoxysklerol was performed, achieving successful hemostasis. Subsequent sessions of EIS led to complete eradication of the esophageal varices.

Discussion: In cases where standard diameter endoscopes cannot be used because of stenosis or other anatomical obstacles, ultra slim endoscopes are often the only alternative, although therapeutic options are limited by the narrow working channel. The EG-840TP combines a slim shaft with a 3.2 mm wide channel, enabling the use of therapeutic devices.

Conclusion: The slim therapeutic upper gastrointestinal endoscope may be extraction option in treating pediatric cases with esophageal varices.

Steep Declining Trends of Hepatitis Virus Prevalence in Mongolia Over the Last 20 Years, a Nationwide Study

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Over the past two decades, Mongolia has achieved a significant reduction in the prevalence of hepatitis viruses, particularly hepatitis B and C. This improvement is closely linked to nationwide early detection programs, vaccination strategies, and access to effective antiviral treatment. This study analyzes trends in hepatitis virus prevalence in Mongolia using population based early screening data collected between 2002 and 2025.

Introduction: Mongolia has long been recognized as a high prevalence country for viral hepatitis. Chronic hepatitis B and C have been major causes of liver cirrhosis and hepatocellular carcinoma, placing a considerable burden on public health. In response, the government implemented comprehensive strategies focused on prevention, early detection, and treatment.

Methods: Aggregated data from PubMed and national programs were analyzed. Hepatitis virus prevalence was expressed as prevalence among apparently healthy population and compared across four periods: 2002 to 2005, 2013, 2017 to 2018, and 2022 to 2025.

Results: Hepatitis virus prevalence declined steadily from 23.8% in 2002 to 2005 to 21.7% in 2013, 13.7% in 2017 to 2018, and 3.2 in 2022 to 2025, representing an approximately sevenfold reduction over two decades.

Discussion: This decline is attributable to universal neonatal hepatitis B vaccination, large scale adult screening programs, the introduction of DAA for HCV, and improved infection control and blood safety.

Conclusion: Hepatitis virus prevalence in Mongolia has decreased markedly due to effective early detection and prevention strategies. Continued targeted screening and treatment are essential to achieving national hepatitis elimination goals.

Routes of New Viral Hepatitis Infections in Modern Mongolia

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Mongolia has one of the highest global burdens of hepatitis B (HBV) and C (HCV) infections, which are the primary drivers of liver cirrhosis and hepatocellular carcinoma. Identifying transmission routes of new cases is essential for prevention and achieving the WHO 2030 hepatitis elimination goal. This study analyzed the causes of infection in 398 newly detected cases (HBV: 154, HCV: 244) based on 2025 epidemiological data. Of the total cases, 317 patients (79.6%) reported a known source of infection, while 81 (20.4%) did not. Among those with identified causes, the leading routes were iatrogenic: cosmetic procedures (65 cases, 20.5%), tattoos (53 cases, 16.7%), and dental treatment (37 cases, 11.7%). These three categories alone accounted for approximately 49% of identified transmissions. HCV cases outnumbered HBV cases (244 vs 154; ratio 1.58:1), with HCV showing greater association with cosmetic procedures (39 vs 26) and tattoos (32 vs 21). Familial transmission was more frequent in HBV (15 vs 21 cases). The findings demonstrate that iatrogenic transmission through inadequately sterilized medical, cosmetic, and tattoo procedures remains the dominant route of new hepatitis infections in Mongolia. The higher proportion of HCV aligns with its predominantly bloodborne nature, while the notable rate of unknown sources (20.4%) underscores gaps in epidemiological tracing. These results emphasize the urgent need to strengthen infection control standards in healthcare facilities, enforce strict sterilization in non medical settings such as tattoo and cosmetic services, and enhance public awareness.

Alcohol Consumption and its Association with HCC in Mongolia according to A-HOC Study

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HCC is a leading cause of death in Mongolia, linked to viral hepatitis and harmful alcohol use. This study analyzed gender, age, and mortality in alcohol-related hepatocellular carcinoma (HCC) using clinical data. 88.8% of cases were male, 11.2% female; peak incidence occurred at 56 to 65 years. Mortality was highest in middle-aged and older groups. Results stress the need for alcohol reduction, early detection, and prevention targeting high-risk populations.

Introduction: HCC is a top global cancer killer. Mongolia has extremely high HCC rates due to hepatitis B/C, alcohol abuse, and metabolic issues. Chronic alcohol leads to steatosis, hepatitis, cirrhosis, and HCC. Alcohol remains common in Mongolia, but detailed local data on alcohol-related HCC patterns are scarce. This study describes these features from routine clinical records.

Methods: Observational study using APASL (A-HOC) surveillance data from real-world clinical records of alcohol-related HCC cases, including gender, age, and mortality. Data stratified by gender/age, presented as percentages and graphs.

Results: 88.8% of cases were male. Highest incidence in 56 to 60 and 61 to 65 age groups; rare below 50, sharp increase after. Mortality mainly in 56 to 65 years, overwhelmingly male. Reflects higher male alcohol use and long-term cumulative liver damage progressing silently to cancer.

Conclusion: Alcohol drives liver cancer in Mongolia. Alcohol-related HCC mainly affects males aged 56 to 65 with high mortality. Urgent actions required: reduce alcohol consumption, target early detection at middle-aged men, and regularly monitor chronic liver disease patients.

Association of HbA1c with Liver Steatosis and Fibrosis in Mongolia

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Background: Diabetes mellitus and insulin resistance play key roles in the development and progression of hepatic steatosis. HbA1c reflects average blood glucose over three months and is widely used in clinical practice, but its relationship with liver steatosis and fibrosis not assessed in Mongolia. This study evaluated the association between HbA1c levels and liver steatosis and fibrosis.

Methods: Among 984 individuals who underwent HbA1c testing at Happy Veritas Hospital (2024 to 2025), 211 subjects aged 28 to 77 years with available steatosis and fibrosis data were included. Liver steatosis and fibrosis were assessed non invasively using Elastography. Steatosis was graded by controlled attenuation parameter (CAP): normal (0 to 240 dB/m), mild, moderate, and severe. Fibrosis was staged by liver stiffness measurement (LSM): F1, F2, F3, and F4. HbA1c categories were normal (less 5.7%), prediabetes (5.7 to 6.4%), and diabetes (above 6.5%).

Results: The mean age was 52.4 years, and mean HbA1c was 6.27%. HbA1c showed a moderate positive correlation with liver steatosis ($r=0.359$) and a weak but significant correlation with liver fibrosis ($r = 0.187$, $p = 0.007$). Body mass index was strongly associated with steatosis, whereas age was significantly associated with fibrosis.

Conclusion: Higher HbA1c levels were significantly associated with increased liver steatosis and fibrosis. Structural liver changes may occur as early as the pre diabetes stage, suggesting that HbA1c may serve as a useful biomarker for early detection and risk stratification of progressive NAFLD.

Stability and Variability of Symptom Burden in Primary Biliary Cholangitis: Insights from a Decade of Follow-Up

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Background: Primary biliary cholangitis (PBC) is associated with impaired health-related quality of life (HRQOL), yet long-term trajectories of patient-reported symptoms in real-world clinical practice remain insufficiently characterized. We examined current symptom burden, longitudinal changes in PBC-40 scores over 10 years, and their clinical relevance in Japanese patients with PBC.

Methods: We performed three complementary analyses: (i) a 2025 cross-sectional analysis (n = 239) assessing associations among PBC-40 domains, EQ-5D-5L, and clinical variables; (ii) a longitudinal comparison of PBC-40 scores obtained in 2015 and 2025 (n = 71); and (iii) an outcome analysis evaluating whether baseline (2015) PBC-40 scores were associated with survival through 2025 (n = 410).

Results: In 2025, moderate to severe impairment was observed in 20-50% of patients across PBC-40 domains. EQ-5D-5L scores were significantly reduced in women younger than 60 years compared with population norms. Multivariable analysis demonstrated that itch, fatigue, and social domains independently contributed to impaired HRQOL. Although median 10-year changes in PBC-40 scores were modest, significant deterioration was observed in the symptoms, itch, and cognitive domains, with substantial inter-individual variability, particularly for itch. Female sex, younger age at diagnosis, ALP normalization, higher ALBI grade, and prior clinical events were associated with worsening itch. Baseline PBC-40 scores were not associated with mortality or liver transplantation.

Conclusions: Long-term symptom trajectories in PBC are heterogeneous, and deterioration of specific domains-especially itch-may occur despite stable overall HRQOL scores. These findings underscore the importance of longitudinal symptom assessment and individualized symptom-oriented management in routine PBC care.

**A-HOC (APASL Hepatology/Oncology Consortium):
A Foundational Dataset for Future Hepatology and Oncology Research**

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Background and Aims: Hepatocellular carcinoma (HCC) remains a major public health challenge in the Asia-Pacific region. Heterogeneity in disease etiology and disparities in healthcare systems impede the implementation of standardized clinical management. The A-HOC study, led by the APASL, was initiated to characterize the etiology, treatment patterns, and clinical outcomes of HCC across the region and to establish a foundation for future research.

Methods: A multinational registry was established through the participation of medical institutions from multiple countries using standardized data collection procedures. Patient enrollment is ongoing for individuals diagnosed with HCC between 2013 and 2027. More than 100 clinical variables, including demographic characteristics, disease etiology, treatment modalities, and outcomes, are systematically collected. The registry was designed as a foundational dataset to enable future subgroup analyses and exploratory research.

Results: As of December 15, 2024, a total of 9,229 patients with HCC had been registered from 47 institutions across 9 countries or regions. For the present analysis, Asia was stratified into six geographic regions (North, West, East, Japan, South, and Southeast), and regional characteristics across multiple clinical parameters were reviewed, revealing heterogeneity in etiological profiles and treatment patterns.

Conclusions: These findings highlight the limitations of uniform international guidelines and emphasize the need for region-specific strategies tailored to local epidemiological backgrounds and healthcare infrastructures. The A-HOC study provides a critical platform for future ecosystem-based analyses and artificial intelligence (AI)-driven research aimed at optimizing HCC management. This collaborative registry is expected to serve as a cornerstone for evidence-based policymaking and the development of regionally adapted clinical practice guidelines.

A-HOC Study on 1108 Patients Under Surveillance for Liver Cancer in Mongolia

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In Mongolia, HCC is a major health issue and has a high prevalence due to its association with chronic infections of viruses such as HBV and HCV. This study analyzed the age distribution, tumor status, cirrhosis status, treatment modalities, surveillance outcomes, and causes of death among patients under surveillance for HCC.

Methods: The study was conducted prospectively and retrospectively. A total of 1,108 cases were selected and analyzed from the registries of HCC patients at Happy-Veritas Hospital and 3 other hospitals. Patients were classified by age group, tumor type (primary/recurrent), cirrhosis status, treatment modality, and surveillance outcome (alive, deceased, lost to follow-up), and actual counts and percentages were calculated.

Results: The age distribution of patients under surveillance is shown in actual numbers. The majority of patients fall into the 60 to 85 age group. The presence or absence of LC was compared in actual numbers and percentages: 59.3% of patients with cancer have liver cirrhosis. The majority (61.7%) of patients under surveillance have recurrent cancer. The vast majority (97.5%) of patients have received some form of treatment. 83.4% of patients under surveillance are still alive. The main cause of death is liver cancer (85.5%). The most common treatment modality is TAE/TACE (16.8%).

Conclusion: Treatment coverage is good (97.5% received treatment), but the primary cause of death remains the cancer itself. There is need to improve survival rate.

Clinical and Epidemiological Analysis of Liver Cancer Patients Under Primary Health Care Center Surveillance in Mongolia

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Background: HCC is one of the leading causes of cancer related mortality in Mongolia and is closely associated with the high prevalence of chronic hepatitis B and C virus infections. We aimed to comprehensively analyze the demographic, clinical, and biochemical characteristics of HCC patients registered under the surveillance of 69 primary health care organizations and to identify differences between early- and late-stage detection of the disease.

Methods: Data from 220 patients were extracted from an Excel-based database and analyzed. Patients were classified according to tumor stages and grouped into early detection and late detection. Comparative analyses were conducted based on age, sex, viral markers (HBsAg, HCV Ab), lifestyle factors, biochemical parameters (AFP, ALT, AST), and geographic distribution.

Results: Of the study population, 60% were male, with a mean age of 65.2 plus minus 10.3 years. HBsAg positivity was observed in 70% of patients, while 30% were anti-HCV positive. Early stage detection accounted for 32% of cases, late stage detection for 32%, and 36% of cases had undocumented tumor stage. Mean levels of AFP, ALT, and AST were significantly lower in patients diagnosed at an early stage compared with those diagnosed at a late stage. Early detection was more frequent in urban settings, whereas late-stage detection predominated in rural areas.

Conclusion: The insufficient rate of early detection of HCC highlights the need to strengthen screening programs and surveillance systems at the primary health care level.

Clinical Characteristics and Survival Outcomes of Hepatocellular Carcinoma at Dr. Moewardi Regional Tertiary Referral Hospital, Indonesia: A Retrospective Study

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Background: Hepatocellular carcinoma (HCC) in Indonesia is often diagnosed at advanced stages, limiting curative treatment and resulting in poor outcomes (30% one-year survival). We aimed to assess the survival outcomes of HCC patients treated at Dr. Moewardi Regional Hospital, Central Java, Indonesia in 2024 until 2025. **Methods:** We retrospectively reviewed 166 HCC patients who checked their illness between January 2024 and September 2025 at a tertiary referral center in Indonesia. Data on BCLC stage, treatment modality, and survival were analyzed.

Result: In this study, only 18% of hepatocellular carcinoma patients received curative or locoregional therapy, while 82% were managed with supportive care. The 1-year survival rates declined with advancing BCLC stage: 100% in A, 82% in B, 63% in C, and 18% in D. Kaplan Meier analysis showed significantly longer survival in patients receiving curative or palliative therapy (75%) compared to supportive care (41%). Among treatments, TACE achieved the highest survival (approximately 85%) and lowest early mortality compared to lenvatinib or best supportive therapy. RFA, liver resection, and sorafenib could not be analyzed due to small sample sizes.

Discussion: Survival outcomes remain poor, primarily due to the predominance of late stage disease and limited access to curative treatment. These findings underscore an urgent need for national HCC screening and early detection efforts (especially targeting HBV carriers) and improved access to curative interventions to enable earlier diagnosis and improve survival outcomes.

Discrepancy between the Real Clinical Status of Patients with HCC and Expectations from HCC Surveillance: A Single Center Study

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For the past 20 years, the Ministry of Health and welfare of Korea has mandated that all target populations participate in the National Liver Cancer Surveillance Program (NLCSP). However, many patients with recently diagnosed HCC are still found at advanced stage, despite the expectations of HCC surveillance testing. Therefore, to evaluate the real clinical situation of HCC surveillance, we investigated severity in patients with HCC and the diagnostic environment. From January 2015 to December 2023, all patients who were diagnosed with HCC in a single hospital in Daejeon, South Korea were retrospectively enrolled in this study. Severity of HCC was evaluated by the Barcelona Clinic Liver cancer (BCLC) staging system. During the course of 9 years, 606 patients were enrolled. The proportion of patients according to BCLC stages were as follows: BCLC-0, 57 patients (9.4%); BCLC-A, 85 patients (14.0%); BCLC-C, 273 patients (45%); and BCLC-D, 138 patients (22.8%). The diagnostic environments were as follows: 39 patients were in the NLCSP group (6.4%), 232 in the group with presenting signs (38.3%), 223 in the regular outpatient care group (36.8%), and 112 patients in the incidental diagnosis group (18.5%). Most patients (67.8%) had advanced stage HCC at diagnosis, and curative treatment was not indicated due to the severity of disease. Therefore, the real clinical situation is far worse than the theoretical expectation of HCC surveillance, suggesting that many high-risk patients for HCC are missed in surveillance.

Combined Assessment of Ferritin, AFP, and PIVKA-II in the Diagnosis of Hepatocellular Carcinoma

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HCC is a leading cause of cancer-related mortality worldwide, often diagnosed at advanced stages. AFP is the standard biomarker for HCC surveillance, but its sensitivity is limited when used alone. PIVKAII enhances diagnostic accuracy when combined with AFP. Serum ferritin, reflecting hepatic inflammation and iron overload, is frequently elevated in HCC patients. We hypothesized that integrating ferritin with AFP and PIVKAII could improve HCC risk stratification and early detection.

Methods: From 8,000 adult patients tested for PIVKAII and AFP at Happy Veritas Hospital, 194 individuals with concurrent serum ferritin measurement were included. Participants were divided into normal and elevated ferritin groups. Results were reported as mean, standard deviation. HCC risk was categorized using established cutoffs: AFP above 10 and above 400 ng/mL; PIVKA II 50 to 149 and 150 mAU/mL; ferritin above 400 and 1000 ng/mL.

Results: Elevated ferritin strongly correlated with higher AFP and PIVKAII levels, particularly in males, where a 2.45-fold ferritin increase was linked to a 2.14 fold AFP rise and a threefold PIVKAII increase. In the 400 to 1000 ng/mL ferritin group, 72.8% were classified as high HCC risk; in the above 1000 ng/mL group, 22.8% were high risk. In females, ferritin elevation showed stronger age dependence, while PIVKA-II remained mostly normal.

Conclusion: Although not tumor specific, ferritin enhances HCC risk assessment when combined with AFP and PIVKA-II. A multi biomarker panel may improve early identification of high-risk individuals, supporting more effective surveillance and screening strategies in clinical practice.

Clinical Impact of the aMAP Risk Score and Hepatocellular Carcinoma on Outcomes after Rifaximin Therapy for Hepatic Encephalopathy

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Background: Hepatic encephalopathy (HE) frequently recurs despite rifaximin therapy. The age-male-ALBI-platelet (aMAP) risk score is a prognostic marker in chronic liver disease, but its role in predicting HE recurrence, particularly in patients with hepatocellular carcinoma (HCC), remains unclear. This subanalysis evaluated the impact of aMAP score and HCC status on HE recurrence and survival after rifaximin therapy.

Methods: We retrospectively analyzed 145 patients with cirrhosis who initiated rifaximin therapy and recovered to West Haven grade 0. Patients were classified by HCC status (no HCC, concomitant HCC, or prior HCC). HE recurrence and overall survival (OS) were assessed. Multivariable logistic regression analysis included ascites, ammonia level, FIB-4 index, mALBI grade, MELD score, and the aMAP risk score. Receiver operating characteristic (ROC) analysis determined the optimal cutoff for predicting HE recurrence. Cumulative HE recurrence was analyzed using a competing-risk model, and OS was evaluated using the Kaplan-Meier method.

Results: In multivariable analysis, the aMAP risk score was the only independent predictor of HE recurrence. ROC analysis identified a cutoff value of 70.843. In the overall cohort, this cutoff significantly stratified both cumulative HE recurrence and OS. HE recurrence did not differ among HCC categories ($P = 0.68$), whereas OS differed significantly ($P < 0.001$). In patients with HCC ($n = 37$), the aMAP cutoff stratified OS ($P = 0.034$) but not HE recurrence ($P = 0.58$).

Conclusion: An aMAP cutoff derived to predict HE recurrence stratified both recurrence and survival overall, but only survival in patients with HCC, likely due to competing mortality risks.

Hepatic Encephalopathy among HCC Patients Monitored for 2 Years, A-HOC Study

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HCC usually develops on a background of chronic liver disease, and hepatic encephalopathy, a severe complication of liver dysfunction substantially affects patients' quality of life and increases mortality. This study aimed to classify primary liver cancer by etiology, compare the frequency of hepatic encephalopathy across etiological groups, and identify in which group the complication predominates. The retrospective observational study included clinical records of 1108 HCC patients, out of which 216 patients were encephalopathy positive, divided into three etiological groups: HBV-related (n=79), HCV-related (n=106), and non-viral (n=31). Hepatic encephalopathy was diagnosed based on clinical signs and symptoms, laboratory results, imaging findings, and physician documentation. Hepatic encephalopathy occurred most frequently in the HCV-related HCC group (n=106), followed by the HBV-related group (n=79), and was least common in the non-viral group (lowest number among 31 patients). These findings suggest that chronic HCV infection leads to more profound and prolonged liver inflammation, fibrosis, and cirrhosis, resulting in greater impairment of liver reserve function and higher encephalopathy risk. It is likely that HCV does something to the brain according to recent studies done by others. In contrast, non-viral HCC cases often preserve relatively better liver function, contributing to lower encephalopathy frequency. The results demonstrate that etiological classification is a critical determinant of hepatic encephalopathy risk in HCC. Hepatic encephalopathy manifests most frequently in HCV-related cases, moderately in HBV-related cases, and least in non-viral cases. Particular attention and early proactive intervention for encephalopathy are especially warranted in patients with HCV-related HCC.

Current Status of Hypozincemia and Zinc Supplementation in Patients with Hepatocellular Carcinoma at Our Hospital

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Background: Hypozincemia is frequently present in patients with liver cirrhosis, but the relationship between serum zinc levels and disease activity or symptoms in patients with hepatocellular carcinoma (HCC) has not been fully elucidated.

Methods: Morning fasting serum zinc levels were measured in 184 patients with chronic liver disease, including 46 patients with HCC, at our hospital. Symptoms related to hypozincemia were ascertained via questionnaire. Zinc supplementation was also administered to 21 patients with zinc deficiency.

Results: The median serum zinc level in 46 patients with HCC was 58.5 µg/dL (22-94), with 57% (26 patients) having a serum zinc level below 60. In 50 patients with liver cirrhosis without HCC, the median was 66 µg/dL (36-93), and in 87 patients with chronic hepatitis, the median was 77 µg/dL (50-114), demonstrating significantly lower zinc levels in patients with HCC. Symptoms associated with hypozincemia in HCC patients included poor wound healing in 20%, dermatitis in 17%, lethargy in 13%, stomatitis in 10%, and hair loss in 10% (multiple answers). Zinc supplementation therapy in 21 zinc-deficient HCC patients resulted in a significant increase in serum zinc (52 to 58 µg/dL) three months later. There were no changes in ammonia or albumin levels, and treatment is continuing.

Conclusion: HCC patients at our hospital had significantly lower zinc levels and a variety of symptoms than patients with cirrhosis or chronic hepatitis without HCC. A significant increase in serum zinc levels was observed in HCC patients after zinc supplementation therapy.

A Case of Mucosa-associated Lymphoid Tissue Lymphoma of the Liver Recurred with the Subsequent Palatal Lesion

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Background: It is reported that primary hepatic lymphoma accounts for approximately 0.4% of extranodal lymphoma. Furthermore, most of them are diffuse large B-cell lymphoma and hepatic mucosa-associated lymphoid tissue (MALT) lymphoma is rare.

Case presentation: An 85-year-old female patient without previous medical history of chronic liver diseases, was incidentally detected with a 30-mm slightly hypervascular intrahepatic nodule on contrast-enhanced CT in S8 region. She was referred to our department for further evaluation. The hepatic lesion exhibited low and high signal intensity on axial T1 and T2-weighted imaging, respectively. Hyperintense signals were found in the diffusion weighted imaging, while the finding of the Gd-EOB-DTPA in the hepatocellular phase was defect. Gastrointestinal endoscopy and colonoscopy showed no evidence of advanced malignant tumors and either AFP and PIVKA-II was not elevated. The patient chose to undergo hepatectomy and the immunohistochemistry results showed CD20+, CD79a+, CD3-, and bcl-2+, while the proliferation factor measured by Ki67 was 10%, resulting in the diagnosis of hepatic MALT lymphoma. Three months later, she presented with pain in palatal area. Because PET-CT detected with abnormal uptake of FDG-PET in the palatal lesion and neighboring lymph nodes. Finally, the pathological findings with palatal lesion due to immunohistochemistry showed the same result with those of hepatic lesion, diagnosed with recurrence of MALT lymphoma.

Conclusions: This is the first case report of hepatic MALT lymphoma, subsequently recurred with palatal lesion. Although MALT lymphoma is rare and categorized as low-grade lymphoma, it could be one of the important differential diagnoses for liver tumors.

Long-Term Clinical Course of Hepatocellular Carcinoma

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Background/Aims: Hepatocellular carcinoma (HCC) often recurs, requiring lifelong surveillance. We evaluated long-term survival, recurrence, and prognostic factors after curative therapy.

Methods: We retrospectively analyzed 454 patients who underwent initial curative treatment for HCC at our hospital between June 2007 and December 2024 (radiofrequency ablation n=346; resection n=108). Overall survival (OS) and recurrence were estimated by Kaplan-Meier, and multivariable Cox models assessed factors associated with OS and recurrence.

Results: Mean age was 72.6±9.4 years; 311 patients were male. Etiology was HBV (n=27), HCV (n=229), and non-B non-C (n=194). Mean tumor diameter was 3.1±2.2 cm and tumor number 1.2±0.6. OS was 64.1% at 5 years, 39.6% at 10 years, and 30.3% at 15 years. Recurrence was 65.8% at 5 years (local recurrence 20.3%), 81.2% at 10 years (26.0%), and 93.3% at 15 years (26.0%). Non-B non-C cases had lower 5-year OS (55.2% vs 70.6%, P<0.01) and higher 5-year recurrence (73.7% vs 61.1%, P<0.01). In multivariable analysis, M2BPGi >1.7 (HR 4.71, P<0.01), non-B non-C etiology (HR 3.52, P<0.01), and tumor diameter >2.5 cm (HR 2.01, P<0.05) predicted worse OS. AFP >8.2 (HR 1.82, P<0.01), male sex (HR 1.54, P<0.01), and non-surveillance-detected presentation (HR 1.39, P<0.05) predicted higher recurrence.

Conclusions: Long-term survival after curative therapy is achievable, but recurrence continues beyond 15 years, supporting lifelong surveillance. Non-B non-C HCC has poorer prognosis. M2BPGi may predict survival and AFP may predict recurrence.

Chemotherapy for Advanced Hepatocellular Carcinoma at a Community Acute Care Hospital

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Background: The proportion of non-B, non-C hepatocellular carcinoma is increasing, necessitating liver cancer treatment not only in early stages but also for advanced disease.

Objective: To investigate the introduction of chemotherapy for hepatocellular carcinoma, particularly advanced hepatocellular carcinoma, in clinical practice at a community acute care hospital.

Methods: Twenty-two patients with hepatocellular carcinoma who were treated at our hospital and received chemotherapy between April 2018, and December 2025.

Results: Median age was 72 years (range: 58-89 years). Fifteen patients (68.1%) were male, and seven were female. Background conditions included hepatitis B in 2 cases, hepatitis C in 5 cases (including 2 with SVR), MASLD in 5 cases, MetALD in 6 cases, ALD in 2 cases, and AIH in 2 cases. Initial chemotherapy regimens comprised lenvatinib in 5 cases, atezolizumab + bevacizumab in 9 cases, and durvalumab + tremelimumab in 8 cases. Initial chemotherapy responses per RECIST were: CR 0, PR 5, SD 10, PD 7 (ORR 22.7%, DCR 68.1%). Among the 14 patients where chemotherapy change was considered post-initiation due to RECIST PD or adverse events, second-line chemotherapy was actually initiated in 5 (36%).

Limitation: Patient selection may be biased due to the presence of two specialized cancer centers in the local area.

Results: Multiple chemotherapy regimens were selected. Compared to studies evaluating individual chemotherapies, this study included patients with poor liver function and those classified as BCLC A (elderly patients with poor surgical prospects).

Treatment Modalities and Response Patterns in Hepatocellular Carcinoma: Real-World Data from a Turkish Cohort

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Background: The management of hepatocellular carcinoma (HCC) has evolved with the introduction of surgical, locoregional, and systemic treatment options. Real-world data are essential to understand treatment patterns and outcomes beyond clinical trial settings.

Methods: This retrospective observational study included patients diagnosed with HCC in Turkey between 2013 and 2023. Available data on treatment status, treatment modalities, and treatment response were analyzed descriptively.

Results: Among 438 patients, 263 (60.0 percent) were classified as treated, while 175 (40.0 percent) were untreated according to available records. Among treated patients (n=263), single-modality treatment was applied in 176 patients (66.9 percent). These included transarterial chemoembolization (TACE) alone in 57 patients (21.7 percent), liver transplantation alone in 43 (16.3 percent), radiofrequency ablation (RFA) alone in 33 (12.5 percent), surgical resection alone in 24 (9.1 percent), systemic therapy alone in 15 (5.7 percent), and transarterial radioembolization (TARE) alone in 4 patients (1.5 percent). Combination therapy was used in 87 patients (33.1 percent). Treatment response assessment demonstrated complete response in 160 patients (60.8 percent), stable disease in 64 (24.3 percent), progressive disease in 6 (2.3 percent), and partial response in 1 patient (0.4 percent). Response status was unavailable in 32 patients (12.2 percent).

Conclusion: In this real-world Turkish HCC cohort, most treated patients received single-modality therapies, while combination approaches were less frequently applied. Treatment responses varied substantially, reflecting the heterogeneity of HCC management in routine clinical practice and providing valuable insight into current treatment patterns and outcomes in Turkey.

Clinical and Etiologic Characteristics of Hepatocellular Carcinoma in a Turkish Cohort

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Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. National real-world data are essential to define disease characteristics and identify gaps in surveillance and early diagnosis.

Methods: This retrospective observational study included 438 patients diagnosed with HCC in Turkey between 2013 and 2023. Clinical and tumor-related data were obtained from institutional medical records and analyzed descriptively.

Results: Hepatitis B virus was the most common underlying etiology (61.6 percent, n=270), followed by metabolic dysfunction-associated steatotic liver disease (MASLD) (10.3 percent, n=45), hepatitis C virus (9.4 percent, n=41), metabolic dysfunction-associated alcohol-related liver disease (2.1 percent, n=9), autoimmune liver disease (1.1 percent, n=5), other causes (4.5 percent, n=20), and unknown etiology (11.0 percent, n=48). At diagnosis, BCLC stage was 0 in 18 patients (4.1 percent), stage A in 133 (30.4 percent), stage B in 110 (25.1 percent), stage C in 119 (27.2 percent), and stage D in 42 (9.6 percent). Child-Pugh class was A in 55.7 percent, B in 29.7 percent, and C in 14.4 percent of patients. During follow-up, 60.3 percent of patients died, with liver-related causes accounting for 52.5 percent of all deaths.

Conclusion: In this large Turkish HCC cohort, hepatitis B virus remained the leading etiology, while MASLD emerged as an important non-viral cause. The high proportion of patients diagnosed at intermediate or advanced stages highlights the need for improved surveillance strategies and earlier detection of HCC in Turkey.

Ectopic Retroperitoneal Hepatocellular Carcinoma Mimicking GIST with Portal Vein Tumour Thrombosis

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Background: Ectopic hepatocellular carcinoma (HCC) arising outside the liver parenchyma is extremely rare and frequently misdiagnosed. We report a case of retroperitoneal ectopic HCC presenting with portal hypertension, portal vein tumour thrombosis, and secondary hepatic involvement.

Methods: A 71-year-old man with diabetes and chronic kidney disease presented with anemia, abdominal discomfort, and upper gastrointestinal bleeding. Endoscopy demonstrated large oesophageal varices. Abdominal ultrasound and serial contrast-enhanced CT scans were performed. Ultrasound-guided biopsies were obtained from the retroperitoneal mass and a focal liver lesion, followed by histology and immunohistochemistry.

Results: Ultrasound revealed a large left retroperitoneal mass (14 x 11 cm), portal vein thrombosis, and small focal liver lesions. CT demonstrated a heterogeneously enhancing hypervascular retroperitoneal mass (11.7 x 12.5 x 14.3 cm), compressing the stomach, pancreas and left kidney, with splenic varices and a 1.9 cm segment VII liver lesion, initially interpreted as a gastrointestinal stromal tumor. Follow-up CT showed tumour progression (12 x 13 x 16 cm), portal vein thrombosis consistent with tumour invasion, new hepatic lesions, splenomegaly, and ascites. Serum alpha-fetoprotein was normal despite AFP-positive tumour on immunohistochemistry. Histology of both the retroperitoneal mass and liver lesion showed trabecular and pseudoglandular hepatocellular morphology with HepPar-1 and AFP positivity and CK7/CK20 negativity, confirming hepatocellular carcinoma with hepatic metastasis.

Conclusions: This case represents a rare ectopic retroperitoneal hepatocellular carcinoma with portal vein tumour invasion and secondary liver involvement, masquerading as GIST on imaging. Recognition of this entity and confirmation with immunohistochemistry are essential for accurate diagnosis and appropriate oncologic management.

Diversity of Imaging Features in Intrahepatic Mass-forming Cholangiocarcinoma Across Different Background Liver Conditions

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Background / Aim: Intrahepatic mass-forming cholangiocarcinoma (IMCC) shows considerable radiologic heterogeneity, yet the influence of background liver condition such as normal liver (NL), chronic hepatitis (CH), or cirrhosis (LC), on its imaging phenotype remains unclear. This study aimed to evaluate whether IMCC imaging features vary according to underlying liver status.

Materials and Methods: Thirty-six pathologically confirmed IMCCs were retrospectively reviewed and classified by background liver condition (NL, n=12; CH, n=13; LC, n=11). Imaging assessments included CT, MRI, and FDG-PET (SUVmax), with additional evaluation of vascular and biliary involvement. Groupwise comparisons used nonparametric and χ^2 -based statistics.

Results: Across the three liver-background categories, no significant differences were observed in major imaging features, including enhancement pattern, delayed contrast characteristics, FDG uptake, capsular features, biliary or vascular involvement, hepatobiliary-phase signal abnormality, tumor size, or multiplicity. SUVmax tended to be higher in IMCCs arising in NL, but without statistical significance. Clinical variables were largely similar except for sex distribution. Initial management showed more frequent resection in CH and fewer in LC, reflecting hepatic reserve rather than imaging phenotype.

Conclusion: IMCC displays substantial imaging heterogeneity, but this variability does not differ meaningfully among NL, CH, and LC. These findings suggest that IMCC radiologic phenotype is determined predominantly by intrinsic tumor biology rather than underlying liver condition.

Clinical Feasibility of Automated Image-Based Registration-Supported Ultrasound-CT Fusion and Its Patient-Dependent Limitations

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Background: Automated ultrasound-CT fusion has emerged as a promising technique to support lesion targeting in liver imaging, yet its realworld feasibility across operators and patient conditions remains insufficiently characterized. This study prospectively examined how well an automated registration system performs in daily practice, focusing on workflow reliability and anatomical factors influencing its stability.

Methods: Eighty four consecutive patients requiring liver ultrasound and recent contrast enhanced CT were evaluated. Three operators with different experience levels performed automated fusion using standardized 3D ultrasound sweeps. No manual correction was permitted. Fusion stability was assessed by comparing projected vascular landmarks with real-time ultrasound findings. Registration precision, completion rate, and procedure time were recorded. Patient characteristics potentially affecting system performance were analyzed using regression models.

Results: The automated workflow consistently produced usable fusion images in most examinations, with successful completion in over 85% of cases across operators. Although more experienced operators achieved finer alignment, the system allowed less-experienced users to generate diagnostically acceptable fusion in the majority of patients. Increased depth from skin to liver capsule emerged as the strongest limiting factor, showing a clear relationship with reduced registration stability. Other clinical variables demonstrated minimal influence on system performance.

Conclusion: Automated fusion substantially streamlines US-CT alignment and reduces operator dependence, making high quality fusion accessible to a broader range of clinicians. However, patient habitus, particularly increased superficial tissue thickness, remains a major barrier to optimal performance. Pre examination assessment of anatomical conditions may help identify cases requiring alternative approaches or manual adjustment.

ADC Increase as a Biomarker of Tumor Shrinkage and PIVKA-II Decline after SBRT in Hepatocellular Carcinoma: A Prospective Study

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Aims: Stereotactic body radiotherapy (SBRT) achieves high local control in hepatocellular carcinoma (HCC), but response is usually evaluated by morphologic criteria. The apparent diffusion coefficient (ADC) from diffusion-weighted magnetic resonance imaging reflects necrosis and cellularity, while alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II) capture biological activity. This prospective study examined relationships among ADC, biomarkers, and treatment responses after SBRT.

Methods: Nineteen patients with 29 HCC lesions received SBRT at 40 Gy in four fractions. MRI with ADC maps, AFP, PIVKA-II, and indocyanine green retention at 15 min (ICG15) were measured at baseline and 1, 3, and 6 months. Tumor response was assessed by modified Response Evaluation Criteria in Solid Tumors. Correlation analyses and logistic regression were performed.

Results: ADC increased significantly post-SBRT. Change in ADC significantly correlated with tumor shrinkage and PIVKA-II decline, but not with AFP. AFP showed no association with ADC, PIVKA-II, or size. Larger tumors required greater planning target volumes, which were linked to ICG15 elevation, suggesting reduced hepatic reserve. Logistic regression identified ICG15 change at 3 months as an independent predictor of complete response (CR; odds ratio 0.93, $p = 0.016$). Local control was high with CR in 3/29, 15/29, and 25/29 lesions at 1, 3, and 6 months, respectively. No grade >2 toxicity or radiation-induced liver disease occurred.

Conclusions: ADC elevation paralleled tumor shrinkage and PIVKA-II decline, supporting their combined utility as early biomarkers of SBRT response. AFP was uninformative, while ICG15 reflected irradiated volume rather than tumor control.

Predictors of Compensatory Hepatic Hypertrophy following Carbon Ion Radiotherapy in Hepatocellular Carcinoma and its Association with Long-term Clinical Outcomes

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Background: This study aimed to investigate predictors of compensatory hepatic hypertrophy and their association with prognosis in patients undergoing carbon ion radiotherapy (CIRT).

Methods: In this retrospective analysis, we included 94 patients with hepatocellular carcinoma (HCC) who received CIRT at Gunma University between November 2010 and June 2020. Significant compensatory hypertrophy was defined as an increase of more than 50 cm³ in the hepatic lateral segment volume at 3 months after CIRT.

Results: The median age of the patients was 76.5 years (IQR, 69.0-83.0), and 63 (67.0%) were male. The median volume of the lateral segment was 254 cm³ (IQR, 183-354), and the median clinical target volume (CTV) was 72.52 cm³ (IQR, 33.69-148.75). An increase in volume after CIRT was observed in 74 (78.7%) patients, whereas a decrease was noted in 20 (21.3%). Significant compensatory hypertrophy was observed in 27 (28.7%) patients. Patients with significant compensatory hypertrophy had larger tumor diameters and CTV values than those without hypertrophy ($p = 0.03$ and $p = 0.01$, respectively). The median overall survival was 87.3 months in patients with significant compensatory hypertrophy and 88.8 months in those without, with no significant difference between the groups ($p = 0.5$). In contrast, patients without worsening ALBI score had significantly better survival than those with worsening ALBI score ($p = 0.004$).

Conclusions: Compensatory hypertrophy was frequently observed after CIRT in HCC patients but was not associated with prognosis. Preservation of liver function appears to be important for achieving a favorable prognosis.

The Roll of Cyber-knife Treatment on Advanced Hepatocellular Carcinoma

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Background: CyberKnife (CK) is a form of stereotactic body radiation therapy that offers high local control, particularly for small sized hepatocellular carcinoma (HCC). The purpose of this study was to examine the prognosis of patients with advanced HCC who received systemic drug therapy and subsequently had CK added to their treatment regimen.

Methods: We retrospectively analyzed 253 patients with advanced HCC who started systemic drug therapy between July 2012 and June 2024. Among these patients, 34 received CK as an additional treatment, while 219 did not. The baseline characteristics of both groups were balanced using propensity score matching. The primary endpoint was cumulative survival rate, and we also evaluated factors affecting survival.

Results: After propensity score matching, there were 25 patients in each group, and no significant difference in patient characteristics was observed. The median cumulative survival was 5.7 years for the CK group and 2.2 years for the control group as median with statistically significant difference ($P = 0.018$). Multivariate analysis showed that the addition of CK was a significant factor contributing to survival (HR 0.41, $P = 0.02$). All patients had other lesions present at the time of CK administration. CK was performed on a total of 51 tumor nodules, with a 100% local control rate.

Conclusion: In patients with advanced HCC who are candidates for systemic drug therapy, the addition of CK is considered a safe and effective treatment for achieving better local control and prognosis.

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Efficacy and Safety of Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma in BCLC Stage A

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Background/Aims: We evaluated the efficacy and safety of stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC) patients who were ineligible for hepatic resection or ablation due to comorbidities or poor general condition.

Methods: Between April 2020 and June 2024, 17 patients (BCLC Stage A; single tumor or ≤ 3 tumors, ≤ 3 cm) out of 44 SBRT recipients were retrospectively analyzed. Endpoints included local control rate (LCR), overall survival (OS), and changes in liver function.

Results: The median age was 77 years (51-93). Reasons for SBRT included poor performance status (PS) ($n=5$), comorbidities ($n=5$), difficulty in RFA ($n=3$), TACE refractoriness ($n=2$), and patient preference ($n=2$). The median dose was 60 Gy in 10 fractions. The median local control period was 22 months, with 1-, 2-, and 3-year LCRs of 100%, 59%, and 44%, respectively. The median OS was 28 months, with 1-, 2-, and 3-year OS rates of 88%, 81%, and 81%, respectively. No significant deterioration in ALBI scores was observed at 1, 3, or 6 months post-treatment. LCR tended to be higher in patients with tumors ≤ 2 cm (BCLC stage 0) compared to those > 2 cm.

Conclusions: SBRT provided favorable local control without significant decline in liver function, even though over half of the patients had poor PS or comorbidities. SBRT is a viable treatment option for HCC patients ineligible for standard local therapies, including high-risk RFA or TACE-refractory cases.

Stereotactic Body Radiation Therapy for Intrahepatic Lesions of Hepatocellular Carcinoma

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Background: Stereotactic body radiation therapy (SBRT) is administered for intrahepatic hepatocellular carcinoma (HCC) treatment. We investigated the safety and efficacy of SBRT for intrahepatic HCC.

Methods: Subjects were patients who underwent SBRT (CyberKnife®) for intrahepatic HCC between April 2014 and September 2025. Background data and tumor/treatment status were collected. We also examined the safety of this treatment.

Results: We treated 114 cases. There were 87 males and 27 females, with a median age of 78 years (range 44-90 years). The etiologies were HCV in 66 cases, HBV in 13 cases, Non-viral in 35 cases. Child-Pugh classification was A in 96 cases, B in 15 cases, and C in 3 cases. BCLC stage was early in 5 cases, intermediate in 27 cases, advanced in 79 cases, and terminal in 3 cases. The median tumor diameter was 26 mm (range 8-56 mm). The number of stereotactic radiotherapy sessions ranged from 3 to 10 (median 5 sessions), and the median radiation dose was 40 Gy (range 25-75 Gy). Among the 84 cases where local treatment response could be assessed, there were 55 complete responses (CR), 21 partial responses (PR), 6 stable diseases (SD), and 2 progressive diseases (PD). Pre-treatment and post-treatment (1, 3, 12 months) liver reserve function markers were: albumin 3.6 ± 0.5 , 3.6 ± 1.9 , 3.7 ± 1.9 , 3.7 ± 1.8 ; total bilirubin 1.0 ± 0.7 , 1.0 ± 0.4 , 0.9 ± 0.4 , 1.0 ± 0.5 ; and PT% was 89 ± 15 , 88 ± 14 , 87 ± 14 , and 91 ± 12 , respectively.

Conclusion: SBRT for intrahepatic HCC appears to be a safe and effective treatment.

Case Study of Advanced Hepatocellular Carcinoma Treated with Combined Radiation Therapy and Chemotherapy

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Background and Purpose: While there is hope for the efficacy of combining chemotherapy with local therapy, this study aimed to examine the clinical characteristics of cases treated with chemotherapy and stereotactic radiotherapy as the local therapy.

Methods: We investigated the clinical course of cases with advanced hepatocellular carcinoma that underwent both stereotactic radiotherapy and chemotherapy during their treatment course. Cases undergoing radiotherapy between 2018 and 2024 were selected if they also received chemotherapy. Radiotherapy was performed using stereotactic radiosurgery (CyberKnife) with gold markers placed where necessary. Safety and efficacy were evaluated for cases receiving both treatments.

Results: Eleven cases received combined radiotherapy and chemotherapy during the study period. There were 1 female and 10 male patients, with a median age of 74 years (range 57-83 years). The first-line drugs used were lenvatinib in 6 cases and atezolizumab + bevacizumab in 5 cases. The median observation period was 24 months (range 1-77 months). No specific adverse effects likely attributable to the combination of radiation and chemotherapy were identified within the scope of this study.

Discussion: This study found no specific safety or efficacy issues with the combination of radiation therapy and chemotherapy. Future studies should evaluate the safety and efficacy of radiation therapy initiated after chemotherapy.

Conclusion: Radiation therapy, when used in combination with chemotherapy, may be considered as an option among local therapies.

Treatment Outcomes of B-RTO and Subsequent Changes in Hepatic Functional Reserve

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Background/Aim: Balloon-occluded retrograde transvenous obliteration (B-RTO) treats gastric varices and portosystemic-shunt-related hepatic encephalopathy. We evaluated outcomes at our institution and changes in hepatic reserve.

Methods: From May 2013 to June 2025, 33 cirrhotic patients underwent B-RTO; 26 with follow-up were analyzed. B-RTO was performed via the right femoral vein with collateral management by stepwise injection and/or coil embolization, followed by 5% ethanolamine oleate iopamidol (EOI) and repeat venography the next day. Response was assessed by endoscopy/CT. Hepatic reserve was assessed by ALBI score at baseline and 6 months.

Results: Median age was 65 years (48-88); 13 were male. Indications were gastric varices (n=19) and hepatic encephalopathy (n=7). Technical success was 92.3%, and all encephalopathy patients improved clinically. Serum albumin increased from 3.273 to 3.577 g/dL (P=0.008) and ALBI improved from -1.972 to -2.223 (P=0.014); 19/26 (73%) showed improved reserve. Esophageal varices worsened in 17 patients; 16 required endoscopic injection sclerotherapy. New/worsening ascites occurred in 5 patients. Procedure-related adverse events included retroperitoneal hemorrhage from left renal vein injury (n=2) and retroperitoneal abscess due to coil infection (n=1).

Conclusion: B-RTO provided favorable clinical outcomes and was associated with improved hepatic reserve, but frequent variceal exacerbation and ascites require careful surveillance.

Evaluation of Stepwise Indocyanine Green Dosing for Hepatic Segment Visualization in a Mouse Model

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Background: Accurate identification of the resection area is essential for safe hepatectomy for malignant liver tumors. When performing subsegmentectomy, a single glissonean pedicle ligation combined with a single intraoperative indocyanine green (ICG) injection may not provide a sufficiently clear demarcation line. Stepwise ICG administration during progressive vascular ligation could offer more precise segmental or subsegmental identification. Therefore, we conducted a mouse study to assess the relationship between ICG dose and fluorescence intensity and to examine the feasibility of sequential segmental visualization.

Method: ICG was administered in 0.25 µg increments every 2 minutes up to a total dose of 4.5 µg, and the fluorescence intensity of liver was analyzed in vivo. In a separate group of mice, single doses of 0.5, 1, 2, 4, 10, 20, or 200 µg were administered, and fluorescence intensities were compared. In addition, the four hepatic lobes were sequentially ligated, followed by stepwise ICG administration (0.5, 1, 2, 4 µg), to evaluate interlobar fluorescence contrast.

Result: In incremental dosing within a single mouse, fluorescence intensity increased linearly with the administered dose ($R^2 = 0.94$). In the single-dose comparison across separate mice, fluorescence intensity increased proportionally from 0.5 to 4 µg ($p < 0.0001$). However, when doses exceeded 10 µg, hepatic fluorescence reached saturation, and strong fluorescence signals were also observed in extrahepatic tissues. In the sequential-ligation experiment, stepwise ICG administration allowed clear delineation of all four hepatic lobes under fluorescence imaging.

Conclusion: Multiple dose ICG administrations may enhance intraoperative segmental demarcation.

Development of Ultra-Fine 3D Images of Intrahepatic Glissonean Structure

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Background: We generally decide the hepatic resection plane based on demarcation lines and main branches of the hepatic veins and portal veins, which is usually planar. In recent years, the laparoscopic magnified view has revealed the true anatomical boundaries exhibit complex shapes and deviate from planar anatomical boundaries, which can lead to some complications. We will examine the method of morphologically observing the Glissonean terminal branches and the spatial relationship with the hepatic vein and construct 3D data.

Methods: 1. Inject stained Silicone into vessel systems. Thin sections of these specimens are prepared to construct pathological images. 2. Make the liver parenchyma transparent using a clearing reagent. The processed sample is observed using a light sheet microscope. We will reconstruct 3D data from these images using image analysis software.

Result: 1. Pathological images were created using goat liver specimens. The images allow observation of Glissonean 's capsules and their spatial relationship. 3D data is being constructed from the image data, which conditions are being evaluated. 2. 2D images were created and observed using light-sheet microscopy. This image can show some parts of the vascular structure which can be identified. Processing conditions are being evaluated to observe the entire specimen's vascular.

Conclusion: Current research data indicates the boundaries of the Glissonean end are complex and not planar. Detailed planar images have been successfully created, and we consider this a significant achievement that will lead to the construction of 3D images in the future.

Routine Use of Intravenous Acetaminophen Safely Enhances Pain Control After Minimally Invasive Hepatectomies

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Background: Effective postoperative pain control is essential after minimally invasive hepatectomy (MIH) to enhance recovery. Multimodal analgesia is widely used to reduce opioid consumption and related adverse effects. Acetaminophen is commonly included in such regimens; however, its safety and efficacy following MIH remain unclear because of hepatic metabolism. This study evaluated the safety and analgesic efficacy of routine intravenous acetaminophen administration after MIH.

Methods: We retrospectively analyzed 50 patients who underwent MIH. Patients were allocated to either an opioid-alone cohort (Cohort O) or an opioid plus routine intravenous acetaminophen cohort (Cohort A). Postoperative pain was assessed using the numerical rating scale (NRS). Analgesic efficacy was evaluated based on NRS scores, frequency and total dose of rescue opioid use, and incidence of postoperative nausea and vomiting (PONV). Safety was assessed by postoperative hepatic function, focusing on prolonged transaminase elevation.

Results: No significant differences were observed between the cohorts in postoperative hepatic or renal function or systemic inflammatory markers. Cohort A demonstrated significantly lower NRS scores on both POD1 and POD2 compared with Cohort O. Almost all patients in Cohort A required no rescue opioid analgesia, resulting in a significantly lower median number of rescue doses (6 vs. 0, $p = 0.0017$). Even among patients in whom opioid doses were reduced due to PONV, Cohort A maintained significantly lower pain scores.

Conclusions: Multimodal analgesia comprising routine intravenous acetaminophen administration could be safe and effective after MIH, without adverse effects regarding hepatic function.

A Predictive Nomogram for Postoperative Delirium after Hepatectomy for Hepatocellular Carcinoma: Development, Validation, and Clinical Utility Analysis

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Background: Postoperative delirium is a common complication after hepatectomy, particularly in older patients and those with multiple comorbidities. However, risk factors for postoperative delirium after hepatectomy for hepatocellular carcinoma (HCC) are not fully elucidated, and no simple risk prediction tool is available.

Methods: We retrospectively analyzed 397 patients who underwent hepatectomy for HCC between 2018 and 2023. Patients were randomly divided into a training group ($n = 272$) and a validation group ($n = 125$). Postoperative delirium was diagnosed using the Confusion Assessment Method. Univariable and multivariable logistic regression analyses were performed to identify independent risk factors. A nomogram was developed in the training group and validated in the validation group. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), calibration plots, and decision curve analysis.

Results: Postoperative delirium occurred in 78 patients (19.5%). Multivariable analysis identified age over 75 years (OR 3.734, 95% CI 1.917-7.353), diabetes mellitus (OR 2.225, 95% CI 1.130-4.393), and preoperative sleeping pill consumption (OR 3.909, 95% CI 1.844-8.275) as independent risk factors, whereas laparoscopic hepatectomy was associated with a lower risk of delirium (OR 0.233, 95% CI 0.050-0.760). The nomogram showed acceptable discrimination with AUCs of 0.749 in the training group and 0.768 in the validation group. Calibration was good in both groups, and decision curve analysis demonstrated clinical utility.

Conclusions: We developed and validated a simple nomogram to predict postoperative delirium after hepatectomy for HCC. This model may help identify high-risk patients and support targeted delirium prevention strategies.

Redox-Active Compound Accelerates Liver Regeneration and Attenuates Acute Injury in Mouse Models: Relevance to Liver Tumor Resection

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Background: Preserving hepatic regenerative capacity while limiting hepatocellular injury is critical in the peri-resection management of liver tumors. 6-O-trans-feruloyl catalpol (6FC), a redox-active iridoid glycoside from *Catalpa ovata*, was evaluated for dual pro-regenerative and hepatoprotective activities in mice.

Methods: C57BL/6J mice were orally pretreated with 6FC and subjected to either 70% partial hepatectomy (PHx) or an acute ethanol challenge. Regeneration was assessed by liver-to-body weight ratio and representative proliferation/cell-cycle markers. Acute injury was evaluated by serum aminotransferases (ALT/AST) and liver histology (H&E).

Results: In the PHx model, 6FC enhanced early liver regrowth and increased proliferation-associated markers, consistent with engagement of redox-sensitive signaling that supports hepatocyte priming and recovery. In an additional acute ethanol-induced liver injury model, 6FC pretreatment attenuated hepatocellular damage, evidenced by reduced ALT/AST elevations and improved hepatic architecture on H&E versus vehicle controls.

Conclusions: 6FC supports liver regeneration and mitigates acute toxic injury in mouse models, supporting translational relevance as a peri-resection strategy to preserve functional hepatic reserve after liver tumor resection.

Conversion Surgery for Hepatocellular Carcinoma following Multidisciplinary Treatment

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Recent advances in systemic therapy and locoregional treatments for hepatocellular carcinoma (HCC) have expanded the feasibility of conversion surgery. A middle-aged man with alcohol-related liver disease was referred in February 2023 for multifocal HCC, with a maximum tumor diameter of 5 cm. Tumor markers were elevated (AFP 1281 ng/mL, AFP-L3 26.5%, DCP 649 mAU/mL), while hepatic functional reserve was preserved (Child-Pugh class A, 5 points). Transarterial chemoembolization (TACE) was performed in March 2023, followed by atezolizumab plus bevacizumab from April 2023. Additional locoregional treatments, including stereotactic radiotherapy and radiofrequency ablation, were applied for residual lesions. Tumor markers temporarily improved but rose again by June 2024, accompanied by persistent vascular enhancement on contrast-enhanced ultrasonography (CEUS), prompting additional TACE. Although atezolizumab plus bevacizumab was continued, tumor markers increased again by June 2025, and CEUS continued to demonstrate vascular enhancement. As other lesions were well controlled and liver function remained stable, left hepatectomy was performed. Pathological examination revealed moderately differentiated HCC with extensive treatment-induced fibrosis and only a small residual viable tumor component. Postoperatively, tumor markers improved (AFP 4.3 ng/mL, AFP-L3 0.5%, DCP 44 mAU/mL), systemic therapy was discontinued, and the patient entered a drug-off status. This case demonstrates that effective tumor control with atezolizumab plus bevacizumab in combination with locoregional therapies can enable conversion surgery in advanced HCC. Contrast-enhanced ultrasonography is useful for assessing treatment response in hepatocellular carcinoma; however, after immune checkpoint inhibitor-based therapy, persistent enhancement may not reliably reflect viable tumor, warranting cautious interpretation.

SP2-2 10175

A Case of Conversion Surgery for a Huge Unresectable Hepatocellular Carcinoma with a Pathological Complete Response after Short-term Immune Checkpoint Inhibitor Therapy Ceased by Liver Dysfunction

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Background: Reports of conversion surgery following systemic drug therapy for unresectable hepatocellular carcinoma (HCC) remain scarce. We herein report a case of conversion surgery performed after only 2-cycle immune checkpoint inhibitor (ICI) therapy for unresectable HCC.

Case: A 70-year-old man presented to a local hospital with weight loss and epigastric pain. Imaging examinations revealed a huge HCC occupying the right liver. His background liver was cirrhotic due to alcohol abuse and past hepatitis B virus (HBV) infection. No extrahepatic metastases were present, and he was referred to our department. The tumor was technically resectable by right hepatectomy. However, the ICG-R15 value was 26.2%, which indicated low hepatic reserve, so it was diagnosed to be unresectable. Therefore, a systemic ICI therapy using Atezolizumab + Bevacizumab was started. Due to immune-related adverse events (irAE) with liver dysfunction and rash, only two cycles of atezolizumab + bevacizumab were administered. Two months after start of chemotherapy, follow-up CT revealed that the tumor shrank, and also the liver function was not changed in ICG-R15 value, so S8 segmentectomy was carried out. Pathological examination confirmed complete response (pCR). Six months after the surgery, no recurrence or metastasis are detected without adjuvant chemotherapy.

Discussion: The 2025 HCC guidelines in Japan suggested that local therapy after systemic drug therapy was considered include TACE and RFA, but did not suggest surgery after sufficient response. Conversion surgery after ICI therapy for unresectable HCC can be done with a pathological complete response even after short-term ICI therapy ceased by liver dysfunction.

A Case of Advanced Hepatocellular Carcinoma Responded to Durvalumab Monotherapy, Leading to Conversion Surgery

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We report a patient with advanced hepatocellular carcinoma (HCC) in whom durvalumab monotherapy was effective, leading to conversion hepatectomy. A 70's old man visited our hospital with appetite loss. Laboratory findings revealed remarkably high inflammation and hypalbuminemia. CT revealed an 80 mm hypovascular mass in segment S5/4 of the liver with a 6 mm nodule in the right lung. Needle biopsy led to the diagnosis of CK19-positive HCC. Durvalumab was initiated due to a performance status of 2 and Child-Pugh B. Subsequently, there was rapid normalization of the inflammatory reaction, improvement in the performance status, and the lung nodule became indistinct. A total of 14 courses of durvalumab were administered, and the tumor shrank from 78 mm to 42 mm. Since the tumor was adjacent to the posterior portal branch, treatment was switched to atezolizumab plus bevacizumab. After one course of atezolizumab plus bevacizumab, we continued with seven courses of atezolizumab monotherapy due to proteinuria. The tumor diameter was reduced to 36 mm, and needle biopsy showed partial viability of tumor cells. Although a right anterior segmentectomy was planned, a right hepatectomy was ultimately performed. Pathological examination revealed a pathological complete response.

SP2-4 10104

A Case of Retroperitoneal Metastasis of Hepatocellular Carcinoma Resected Laparoscopically

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An 83-year-old woman with a history of chronic hepatitis C was treated for hepatocellular carcinoma (HCC). In 2015, radiofrequency ablation was performed for an HCC lesion in liver segment 3. She achieved a sustained virological response after treatment with direct-acting antivirals in 2016. Subsequently, she experienced multiple intrahepatic recurrences: laparoscopic subsegmentectomy of segment 8 in 2019 and laparoscopic partial resection of segments 4 and 8 in 2023 for recurrence at the resection margin. In 2025, elevation of serum alpha-fetoprotein (AFP) and AFP-L3 levels was observed. Imaging studies revealed a growing 10-mm tumor protruding caudally from liver segment 6, and recurrent HCC was suspected. Laparoscopic surgery was performed in December 2025. Intraoperatively, the tumor was found to have no continuity with the liver and was identified as a retroperitoneal tumor. As no other lesions were detected and the tumor was solitary, laparoscopic resection of the retroperitoneal tumor was performed. Histopathological examination confirmed metastatic hepatocellular carcinoma. Retroperitoneal metastasis of HCC is rare. Proposed metastatic pathways include hematogenous spread, lymphatic spread, and peritoneal dissemination; however, there is no consensus. In this case, macroscopic findings suggested that peritoneal dissemination was unlikely. We report this rare case with a brief review of the literature.

Multidisciplinary Management for Recurrence after Liver Resection for Hepatocellular Carcinoma

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To clarify the therapeutic efficacy of transarterial chemoembolization (TACE) and systemic therapies for intrahepatic recurrence after liver resection for hepatocellular carcinoma (HCC). A total of 435 patients underwent TACE or systemic therapy for intrahepatic recurrence after liver resection for HCC at our institution. Patients were classified into four groups: TACE alone (n = 277), TACE plus sorafenib (n = 61), TACE plus lenvatinib (n = 58), and TACE plus atezolizumab plus bevacizumab (n = 39). Univariate analysis was performed using the Mann-Whitney U test and the chi-squared test. Overall survival (OS) was estimated using the Kaplan-Meier method and compared using the log-rank test. Prognostic factors were identified using Cox proportional hazards models. Significant differences were observed in hepatitis virus infection (p = 0.01) and macroscopic vascular invasion (p = 0.02). OS was significantly better in the sorafenib group than in the TACE alone group, and significantly better in the lenvatinib and atezolizumab plus bevacizumab groups than in the sorafenib group (p less than 0.001). No significant difference was observed between the lenvatinib and atezolizumab plus bevacizumab groups (p = 0.18). In the Cox proportional hazards model, multivariate analysis identified tumor burden at treatment initiation as a significant prognostic factor. Regarding treatment modality, significant differences were observed among all comparisons except between the lenvatinib and atezolizumab plus bevacizumab groups (p = 0.22). Multimodal therapy combining TACE with lenvatinib or atezolizumab plus bevacizumab improves prognosis in patients with intrahepatic recurrence after liver resection for HCC.

Characteristics of HCV-Related Hepatocellular Carcinoma Patients Achieving Long-Term Cancer-Free Survival after Repeated Hepatectomy in SVR Status

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Eradication of HCV reduces the incidence of HCC; however, HCC can still develop after achieving an SVR. Among them, some patients achieve relatively long-term cancer-free survival after repeated hepatectomy. This study aimed to clarify the characteristics of such patients. Between 2013 and 2022, 105 patients underwent hepatectomy for HCV-related HCC at our institution. Among them, 17 patients who subsequently underwent repeat hepatectomy for recurrence were retrospectively analyzed. Factors potentially associated with cancer-free survival after repeat hepatectomy were evaluated, including SVR status, time to first recurrence, hepatic functional reserve, primary tumor characteristics, recurrence pattern (genomic IM vs. MC), and degree of liver fibrosis. The cohort consisted of 11 men and 6 women. Fifteen patients had achieved SVR before or after the initial hepatectomy, while two remained untreated. Among the 15 SVR patients, 7 achieved a cancer-free status for more than 2 years after the final hepatectomy. In SVR patients, the interval to first recurrence was not significantly associated with cancer-free survival. However, a tendency toward longer cancer-free survival was observed in patients without vp at initial resection, those with MC-type recurrence, preserved liver function, and mild liver fibrosis (F1-2). Notably, one exceptional patient (F1) classified as IM in all four consecutive resected specimens also achieved more than 3 years of cancer-free survival. In conclusion, among patients with HCV-related HCC after SVR, aggressive repeat hepatectomy for recurrent disease can lead to long-term cancer-free survival, particularly in those with preserved liver function, mild fibrosis, absence of portal vein invasion, and MC-type recurrence.

SP3-2 10149

Cure by Liver Transplantation of HCV-related Decompensated Cirrhosis with Hepatocellular Carcinoma Developing 14 Years after IFN-induced SVR

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Background/Aim: Although SVR can improve liver function even in HCV-related decompensated cirrhosis, long-term outcomes remain unclear. We report a rare patient in whom general status was relatively stable for 14 years after IFN induced SVR, who then developed HCC, but ultimately underwent curative liver transplantation.

Case: A 54 year old man, given a blood transfusion at age 3, was diagnosed with early liver cirrhosis (Child-Pugh A) at age 26. His HCV-RNA was 7×10^6 copies/mL, genotype 1b. Viral clearance failed with conventional IFN therapy. At age 35, he progressed to Child-Pugh B, and low dose intermittent Peg-IFN α 2a was administered for 34 months until treatment discontinuation due to refractory ascites (Child-Pugh C). Although ascites persisted for 20 months, viral clearance was achieved upon resolution, and SVR was subsequently maintained. Fourteen years after completing SVR, CT revealed a 32 mm multinodular confluent HCC in segment 3, prompting hospitalization. Due to impaired hepatic reserve and severe portal hypertension (Child-Pugh 10C, MELD 12), curative local therapy was not feasible. He underwent bridging TACE twice while awaiting deceased-donor liver transplantation. After 1.5 years, successful transplantation cured his liver disease.

Conclusion: While clinical stability may be maintained for more than a decade after IFN-induced SVR, once HCC develops liver transplantation is the only curative option. In Japan, with limited access to liver transplantation, achieving favorable long term outcomes in patients with decompensated cirrhosis requires meticulously managing hepatic fibrosis and portal hypertension even after SVR.

ALPPS followed by Salvage LDLT for Recurrent HCC

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Background: Hepatocellular carcinoma (HCC) associated with chronic hepatitis B and cirrhosis remains a therapeutic challenge, particularly in patients with multifocal disease and insufficient future liver remnant (FLR). Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) enables rapid liver hypertrophy, while liver transplantation remains the definitive treatment for selected cases with recurrence.

Case Presentation: A 58 year old male with hepatitis B related cirrhosis was diagnosed with multifocal HCC involving liver segments 6, 7, and 8. Preoperative volumetry revealed an FLR of 31.8%. Laparoscopic ALPPS stage 1 was performed, resulting in rapid hypertrophy with FLR increasing to 54.9% within 14 days. ALPPS stage 2 was subsequently completed without complications. Histopathology demonstrated a well-differentiated T3N0 HCC without portal vein thrombosis, lymphovascular, or perineural invasion. The patient was discharged uneventfully. In June 2025, follow-up imaging revealed multiple intrahepatic recurrent lesions without extrahepatic involvement. Liver function was preserved (Child-Pugh A, MELD-Na 9), and there were no signs of portal hypertension. The patient was therefore evaluated for transplantation and successfully underwent living donor liver transplantation in July 2025. He was discharged on postoperative day 8 without complications.

Conclusion: This case illustrates that ALPPS can be an effective strategy to achieve curative resection in advanced HCC with inadequate FLR. Furthermore, living donor liver transplantation represents a feasible and effective salvage treatment for carefully selected patients with recurrent HCC following complex hepatic surgery.

SP3-4 10215

Immunosuppressive Medication Non-adherence in Liver Transplantation Adult Recipients in Vietnam

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Background: Long-term graft survival after liver transplantation depends heavily on strict adherence to immunosuppressive therapy. Non-adherence remains a major cause of graft dysfunction, rejection, and unplanned hospitalization, yet data from Southeast Asia, particularly Vietnam, are limited.

Methods: A cross-sectional study was conducted among 136 adult liver transplant recipients followed at the Hepato-Biliary and Pancreatic Surgery Department, 108 Military Central Hospital (2017-2025). Adherence was assessed using the validated BAASIS questionnaire. Clinical, demographic, and psychosocial factors were analyzed for associations with non-adherence.

Results: Mean follow-up after transplantation was 25.7 +/- 17.4 months; 83 percent were male and 98.1 percent received living-donor grafts. The overall non-adherence rate was 14.6 percent. Significant determinants of poor adherence included transplant indication ($p = 0.027$), lack of encouragement or feedback from healthcare staff during follow-up ($p = 0.038$), and dissatisfaction with immunosuppressant therapy ($p = 0.001$). Patients with acute liver failure demonstrated the highest adherence rates.

Conclusion: Immunosuppressive adherence among liver transplant recipients in Vietnam is relatively high, though gaps remain. Strengthening post-transplant counseling, structured follow-up communication, and patient-centered medication education could further reduce non-adherence. These findings highlight modifiable behavioral and healthcare-system factors and support the need for multidisciplinary interventions in low- and middle-income transplant settings.

Keywords: liver transplantation, adherence, immunosuppression, BAASIS, Vietnam

A Resected Case of Gallbladder Carcinoma Difficult to Differentiate from Metastatic Gastric Cancer to the Gallbladder

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Background: Differentiating primary gallbladder carcinoma from metastatic gastric cancer to the gallbladder is often challenging, particularly when imaging findings are atypical. We report a case in which preoperative distinction was especially difficult.

Methods: We retrospectively reviewed the clinical course, imaging studies, surgical findings, and pathological examinations of an 85-year-old man previously treated with laparoscopic distal gastrectomy for advanced gastric cancer.

Results: A gallbladder polyp detected four years after gastrectomy enlarged from 13 mm to 19 mm. Contrast-enhanced CT and endoscopic ultrasonography demonstrated a broad-based fundal lesion with a capsule-like appearance, atypical for gallbladder carcinoma and suggesting possible metastatic gastric cancer. Due to interval growth and the inability to exclude malignancy, liver bed resection was performed. The postoperative course was uneventful, with discharge on day 5. Lymph node recurrence developed four months later, and chemotherapy with gemcitabine monotherapy was ineffective, leading to best supportive care. Pathology showed predominantly poorly differentiated adenocarcinoma resembling the prior gastric cancer; however, partial squamous differentiation and focal continuity with intramucosal epithelium supported a final diagnosis of gallbladder carcinoma with subserosal invasion.

Conclusion: This case highlights the diagnostic challenge of distinguishing atypical gallbladder carcinoma from metastatic gastric cancer based solely on imaging and underscores the importance of comprehensive pathological evaluation.

Percutaneous Radiofrequency Ablation in Early-stage Hepatocellular Carcinoma

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Radiofrequency ablation (RFA) is a minimally invasive treatment widely performed for the treatment of liver neoplasms. Recently, resulting of long prognosis has made by ablation in the clinical practice. In Japan, JSH consensus statements and recommendations 2021, Resection and RFA are equally recommended as first-line therapy in patients of less than 3cm, 3 nodules HCC in the result of a head-to-head randomized controlled trial (SURF trial). We introduced adjustable RFA electrode needle (VIVARF system) which became usable from 2015 in order to improve therapeutic results of RFA. In 125 patients with liver cancer. The 5-year survival rate of RFA at our institution is 70%. Although local recurrence rate after curative RFA is as low as 6.0%, the intrahepatic distant metastasis is as high as 70% at 5 years. Complications were skin burned in 4.2% due to cause by needle damage from induction needle. We use a variety of techniques such as artificial pleural effusion, artificial ascites, under sedation to improve the effectiveness of our treatments. After the treatment, the prevention of intrahepatic distant recurrence by direct-acting antivirals (DAAs) is very important.

LTP-2 10035

EUS-Guided Ethanol Injection for Hepatocellular Carcinoma Inaccessible by Percutaneous Approach: A Successful Case of Local Tumor Control

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Background: Radiofrequency ablation (RFA) is a standard local therapy for early-stage hepatocellular carcinoma (HCC). However, deeply located lesions or those with poor percutaneous access, especially in patients with ascites, may increase procedural risk. In Japan, EUS-guided RFA is not approved; therefore, EUS-guided ethanol injection (EUS-EI) is an alternative technique in selected cases.

Case Presentation: A 66-year-old man with alcoholic liver cirrhosis had previously undergone RFA for a 2.0-cm HCC in segment 6. Follow-up EOB-MRI revealed a new 10-mm lesion in segment 1. Because the percutaneous route was technically difficult due to the deep location and moderate ascites, EUS-EI was chosen. After administration of tolvaptan to reduce ascites, a linear scanning ultrasound endoscope (GF-UCT260, Olympus) was used to visualize a 10-mm hypoechoic mass in segment 1 from the esophagogastric junction. A safe puncture line without intervening vessels was confirmed, and 6 mL of absolute ethanol was injected into the lesion. Post-procedural contrast imaging showed complete loss of enhancement, indicating successful local ablation. During 1.5 years of follow-up, no local recurrence or new HCC was observed.

Discussion and Conclusion: Although percutaneous ethanol injection therapy has generally shown higher local recurrence rates than RFA, several studies report comparable outcomes for tumors less than 2 cm. For tumors in anatomically challenging locations or in patients with ascites, EUS-guided ethanol injection may be a feasible and effective local therapy. This case highlights the utility of EUS-EI for achieving local tumor control when percutaneous ablation is not feasible.

Efficacy and Safety of Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma in the Caudate Lobe: A Comparative Study with Radiofrequency Ablation Authors

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Background: This study compared the efficacy and safety of stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) located in the caudate lobe.

Methods: This retrospective study included 57 patients with caudate lobe HCC who underwent either RFA (n = 39) or SBRT (n = 18) at seven institutions in Japan between January 2016 and August 2025. Local tumor progression (LTP), distant recurrence, overall survival (OS), and changes in albumin bilirubin (ALBI) scores were analyzed. Propensity score matching (PSM) was performed to minimize baseline imbalances between the two groups.

Results: The median ages were 74 years in the RFA group and 75 years in the SBRT group; 28 (71.8%) and 12 (66.7%) patients were male, respectively. There were no significant differences in LTP and distant recurrence between the two groups in either the crude cohort (p = 0.856 and 0.622, respectively) or the PSM-matched cohort (p = 0.286 and 0.907, respectively). Although OS did not differ significantly in the crude cohort (p = 0.090), the RFA group demonstrated superior survival compared with the SBRT group in the PSM matched cohort (p = 0.031). No grade 3 or higher adverse events occurred in either group. However, ALBI scores worsened significantly in the SBRT group compared with the RFA group (p = 0.025).

Conclusions: SBRT achieved favorable local control with an acceptable safety profile. It may represent a valuable alternative for patients in whom RFA is technically challenging.

A Propensity Score-Matched Comparison of Particle Therapy and Transarterial Chemoembolization for Hepatocellular Carcinoma

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Background: Particle therapy (PT), including proton and carbon-ion therapy, and transarterial chemoembolization (TACE) are established locoregional treatments for hepatocellular carcinoma (HCC); however, direct comparative evidence between these modalities remains limited. We compared outcomes between PT and TACE using propensity score matching (PSM).

Methods: We retrospectively analyzed 242 patients treated with PT and 135 patients treated with TACE as initial therapy for primary HCC between March 2012 and August 2021. Propensity score matching was performed using age, modified albumin-bilirubin (mALBI) grade, maximum tumor diameter, and des-gamma-carboxy prothrombin (DCP), which differed between the two groups at baseline. Overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan-Meier method and compared by the log-rank test. Treatment subgroup interactions were explored using Cox proportional hazards models with interaction terms.

Results: After PSM, 84 patients were included in each group with well-balanced baseline characteristics. PFS was significantly longer in the PT group than in the TACE group (p = 0.024), whereas no significant difference in OS was observed (p = 0.670). For PFS, TACE was associated with more favorable outcomes than PT in patients with bilobar disease (p less than 0.001). In contrast, for OS, TACE showed a relative advantage over PT in patients with centrally located tumors (p = 0.024).

Conclusions: After PSM, PT and TACE achieved comparable OS, while PT provided superior PFS. Interaction analyses suggest that tumor distribution and tumor location may modify the relative efficacy of PT and TACE, supporting complementary roles of these modalities in the management of HCC.

Exploring the efficacy of Systemic Inflammatory Markers in predicting outcomes post Transarterial Chemoembolization (c TACE & deb TACE)

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Background: Tumour inflammation is the driving force behind tumour progression in hepatocellular carcinoma. Various markers can predict connection between inflammatory response and tumour microenvironment. Systemic inflammatory markers like LMR ratio, SII index, can offer insight into the inflammatory milieu, which may predict the response to locoregional therapy.

Methods: This is an ambispective study done from January 2023 to March 2025 encompassing 43 patients with intermediate stage HCC, undergoing TACE (cTACE & debTACE) for tumour downstaging. Patients were evaluated for biochemical and inflammatory panel, serum AFP levels and imaging prior. Post TACE follow up imaging was done at one and three months to identify response using mRESICT criteria.

Results: Total 43 patients were included in the study. The mean age of the participants was 55.84 \pm 9.87 years consisting of 25.5% females and 74.4% males. The most common etiology was Hepatitis B, followed by MASLD & Hepatitis C. 27.9% patients underwent debTACE and 72.09% patients underwent cTACE. Higher SII ($p=0.041$) and lower LMR ($p=0.024$) were associated with a poor tumour response. The ROC analysis for the LMR predicted treatment outcomes in patients with HCC with a cut-off value of ≥ 2.2 [AUC- 0.892, (95% CI 0.619 -0.976)] having better prognosis. AFP levels also correlated with the outcome to TACE ($p=0.033$) There was no significant difference in the outcome with debTACE as compared to cTACE.

Conclusion: Peripheral inflammatory markers can unveil the dynamics between the tumour biology, microenvironment and immune response, that can be incorporated prior to TACE, paving way for an enhanced therapeutic precision.

Objective Response, Survival, and Downstaging After Yttrium-90 Radioembolization in Intermediate and Advanced Hepatocellular Carcinoma

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Background and Aims: Yttrium-90 (Y-90) transarterial radioembolization (TARE) is an established locoregional therapy for hepatocellular carcinoma (HCC), particularly in intermediate and advanced stages. In the contemporary oncology paradigm, objective tumor response and disease downstaging may translate into improved survival and eligibility for curative treatment. This study evaluated treatment response, overall survival, and downstaging outcomes following Y-90 TARE in patients with Barcelona Clinic Liver Cancer (BCLC) stage B and C HCC at a single tertiary center.

Methods: We retrospectively analyzed patients with BCLC stage B or C HCC who underwent Y-90 TARE as the sole HCC treatment between January 2019 and December 2025. Patients lacking adequate pre-treatment dynamic imaging, lost to follow-up, or diagnosed with non-HCC malignancies were excluded. Tumor response was assessed using modified RECIST (mRECIST) criteria. Overall survival was analyzed according to radiologic response and post-TARE surgical conversion.

Results: A total of 47 patients were included. Objective response was achieved in most patients, with complete response (CR) in 4.3%, partial response (PR) in 68.1%, stable disease (SD) in 10.6%, and progressive disease (PD) in 17.0%. Median overall survival differed significantly by response: 24.0 months for CR, 14.8 months for PR, 13.8 months for SD, and 3.8 months for PD ($P<0.01$). Downstaging to surgical resection after TARE was achieved in 14.9% of patients, all attaining CR.

Conclusions: Y-90 TARE yields high objective response rates and meaningful survival benefit in selected patients with intermediate and advanced HCC. Objective response and successful surgical downstaging are key determinants of favorable outcomes.

Widespread Peritoneal Seeding after Popping Phenomenon during Microwave Ablation for Hepatocellular carcinoma: A Case Report

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Background: Artificial ascites–assisted percutaneous microwave ablation (MWA) for subcapsular hepatocellular carcinoma (HCC) is widely used, but peritoneal metastasis is a rare, serious complication; a popping phenomenon during ablation may contribute in addition to needle–tract seeding.

Case report: A 63-year-old man with hepatitis B–related chronic liver disease had HCC for 18 years and had undergone radiofrequency ablation 18 times. He underwent artificial ascites–assisted percutaneous MWA for a 35–mm posterior subcapsular HCC in segment III adjacent to the stomach. Artificial ascites was created using 1,500 mL of 5% dextrose, and MWA was performed with a single puncture (total ablation time, 13 minutes). A popping phenomenon occurred during ablation, but no apparent increase in echo-free space was observed. Postprocedural hypotension prompted contrast-enhanced CT, which revealed a hematoma in and around the ablation zone without active extravasation. At 3 months post–MWA, contrast–enhanced MRI revealed more than 10 new peritoneal nodules on the liver surface, the lesser omentum, and the gastric and splenic surfaces. Tumor markers were markedly elevated (AFP 112,840 ng/mL; PIVKA–II 1,278 AU/mL). Systemic therapy with atezolizumab plus bevacizumab was initiated. After 6 cycles (8 months after MWA), peritoneal lesions regressed and became radiologically undetectable on contrast–enhanced MRI, and tumor markers normalized. At 12 months after MWA, he remained in complete response per RECIST 1.1 while continuing therapy.

Conclusion: The temporal sequence is consistent with intraperitoneal tumor spillage due to the popping phenomenon, with artificial ascites potentially facilitating widespread distribution of tumor cells. Strategies to prevent popping phenomena are warranted.

Superiority of ICI-Based Regimens Over TKIs in Advanced HCC: A Systematic Review and Meta-Analysis

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Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, with limited therapeutic success in advanced stages. Tyrosine kinase inhibitors (TKIs), such as sorafenib and lenvatinib, have long been standard first-line treatments; however, their modest survival benefits and considerable toxicity underscore the need for more effective alternatives. Immune checkpoint inhibitors (ICIs) have shown encouraging results, yet direct comparisons between ICI-based regimens and TKI monotherapies remain limited.

Methods: A systematic review and meta-analysis were conducted following PRISMA guidelines, with a protocol registered in PROSPERO (CRD420251000417). PubMed, Embase, and CENTRAL were searched for studies comparing ICI-based regimens with TKI monotherapies in patients with advanced or unresectable HCC. Both randomized controlled trials and high-quality observational studies reporting clinical outcomes – including overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) – were included.

Results: Seventeen studies (RCTs and observational studies) comprising patients with advanced HCC were included. Compared with TKI monotherapies, ICI-based regimens significantly improved OS (HR = 0.76; 95% CI: 0.65 – 0.88; I² = 72%) and PFS (HR = 0.71; 95% CI: 0.62 – 0.81; I² = 70%). Furthermore, ICI-based therapies achieved higher ORR (RR = 1.58; 95% CI: 1.09 – 2.29) and DCR (RR = 1.10; 95% CI: 1.00 – 1.20). In terms of safety, ICI regimens were associated with fewer adverse events of any grade and grade 3&ndsh4 severity.

Conclusions: ICI-based therapies demonstrate superior efficacy and tolerability compared with TKI monotherapies in patients with advanced HCC, supporting their growing role as preferred first-line treatment options.

STP1-2 10088

Comparative Outcomes of Immunotherapy plus Transarterial Therapy versus Systemic Therapy Alone in Hepatocellular Carcinoma: A Systematic Review

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Introduction: Hepatocellular carcinoma (HCC) remains a major global health challenge, with many patients presenting at intermediate or advanced stages where curative options are limited. Although immunotherapy and anti-angiogenic agents have improved systemic treatment outcomes, intrahepatic progression continues to compromise long-term survival. Transarterial therapies remain central for liver-dominant disease, prompting increasing interest in their integration with modern immunotherapy.

Objective: To compare clinical outcomes between immunotherapy-based systemic therapy alone and immunotherapy combined with transarterial therapy in intermediate and advanced hepatocellular carcinoma.

Methods: A systematic search of PubMed, Cochrane Library, and ScienceDirect identified comparative studies evaluating PD-1/PD-L1 based immunotherapy administered with or without transarterial therapy, including transarterial chemoembolisation (TACE) or hepatic arterial infusion chemotherapy (HAIC). Outcomes of interest included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and treatment-related adverse events. Data were synthesised narratively in accordance with PRISMA guidelines.

Results: Eight studies met the inclusion criteria. All demonstrated that adding TACE or HAIC to immunotherapy produced longer overall survival, prolonged progression-free survival, and higher objective response and disease control rates. Benefits were consistent across different systemic regimens and were especially notable in high-burden intrahepatic disease and portal vein invasion. Importantly, the incidence of severe adverse events remained comparable between treatment groups.

Conclusion: Combining transarterial therapy with immunotherapy-based systemic treatment offers meaningful survival and response advantages without compromising safety. This multimodal strategy represents a promising approach for selected patients with intermediate or advanced hepatocellular carcinoma, although prospective randomized trials are required to confirm these findings.

COVID-19 Pandemic's Impact on the Global Disease Burden of HBV-related Hepatocellular Carcinoma in the Elderly

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Objective: The disease burden of HBV-related hepatocellular carcinoma (HCC) in the elderly has become a critical public health issue. Using data from the Global Burden of Disease Study (GBD) 2021, this study evaluated the global, regional, and national burden of HBV-related HCC in the elderly, focusing on trend changes before and after the COVID-19 pandemic, as well as differences across Socio-Demographic Index (SDI) categories and genders.

Methods: We analyzed age-standardized incidence and mortality rates (ASIR and ASDR) of HBV-related HCC in the elderly from 1990 to 2021, with emphasis on comparing 2019 to 2021 trends. Joinpoint regression, age period cohort (APC) analysis, decomposition analysis, and nonlinear regression were applied to assess trends, quantify driving factors, and explore associations between key indicators.

Results: Global ASIR and ASDR showed an overall declining trend with significant regional heterogeneity higher in African regions and lower in some American regions. Post-pandemic, the global decline accelerated, though some countries saw rising rates. Males consistently had higher ASRs than females, with faster post-pandemic declines. Epidemiological changes were the primary driver; aging's contribution to incidence increased after 2019. APC analysis revealed age-related risk fluctuations and notable birth cohort differences.

Conclusion: Despite progress in global HBV-related HCC control among the elderly, regional disparities persist, with elderly males bearing a heavier burden. Post-pandemic trends vary by country. Future strategies should prioritize the elderly, especially males, through enhanced screening and personalized treatment, alongside optimized public health measures and comprehensive surveillance systems to reduce the global disease burden.

STP1-4 10031

COVID-19 Pandemic Did not Affect the Treatment Uptake of Immunotherapy as the Treatment for Advanced Hepatocellular Carcinoma (HCC)

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Background: Immunotherapy as the first-line treatment for advanced hepatocellular carcinoma (HCC) has improved outcomes. Yet, in view of the high cost, health inequality issues in treatment access by socioeconomic status are increasingly recognised; the COVID-19 pandemic in 2020-2023 might have further exaggerated these.

Methods: All patients diagnosed with HCC between 2015 and 2024 were identified. Immunotherapy was defined with prescription of atezolizumab (+/-bevacizumab), ipilimumab and nivolumab, tremelimumab and durvalumab, or pembrolizumab; annual proportions used the HCC diagnosis year as the index year, counting immunotherapy prescribed at any time after diagnosis.

Results: 17,210 patients with HCC in 2015-2024 were identified (mean age 67.8 +/- 12.9 years); 1,459 (8.5%) received immunotherapy. Annual uptake increased from 45/1,711 (2.6%) in 2015 to 141/1,764 (8.0%) in 2019, 143/1,679 (8.5%) in 2020, 221/1,710 (12.9%) in 2023 and 210/1,654 (12.7%) in 2024, with no clear interruption during the COVID-19 period. Crude all-cause mortality rates were 0.98 deaths per person-year (456 events over 466 person-years; 95% CI 0.89-1.07) among immunotherapy recipients and 1.33 deaths per person-year (6,426 events over 4,849 person-years; 95% CI 1.29-1.36) among non-recipients. Before 2020, nivolumab and pembrolizumab were predominant; from 2022 onwards atezolizumab regimens were most used (82, 146 and 133 patients in 2022, 2023 and 2024, around 38-59% per year), with increasing use of regimens including durvalumab.

Conclusions: The pandemic did not have a major impact on immunotherapy use for advanced HCC. The impact of dramatic increase in newly approved regimens on clinical outcomes warrants further evaluation.

Early Clinical Outcomes of Nivolumab plus Ipilimumab Combination Therapy for Advanced Hepatocellular Carcinoma

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Background/Aim: We evaluated the early safety and efficacy of nivolumab plus ipilimumab (Nivo/Ipi) combination therapy at our institution.

Methods: This retrospective study included 25 patients with hepatocellular carcinoma (HCC) who initiated Nivo/Ipi between July 1 and September 30, 2025. Patient characteristics and safety profiles, including immune-mediated adverse events (imAEs), were assessed. Efficacy was evaluated in 17 patients who underwent initial radiological assessment.

Results: The median age was 70 years (45 - 83). Child-Pugh class was A5 in 11 patients (44%), A6 in 10 patients (40%), and B7 in 4 patients (16%). 16 patients (64%) were classified as BCLC stage C. Macrovascular invasion and extrahepatic metastasis were each observed in 9 patients (36%). Nivo/Ipi was administered as first-line therapy in 13 patients (52%), second-line in 8 (32%), and third-line or later in 4 patients (16%). ImAEs occurred in 13 patients (52%), most commonly hepatitis (n=8, 32%), dermatitis (n=7, 28%), and colitis (n=2, 8%). More than 80% of imAEs developed within two weeks of treatment initiation, and 7 patients (28%) experienced imAEs involving two or more organs. High-dose corticosteroids were required in 4 patients (16%). Grade 3 or 4 imAEs occurred in 4 patients (16%). Among the 17 patients who underwent initial imaging assessment, 3 (18%) achieved a partial response, 9 (53%) had stable disease, and 5 (29%) showed progressive disease.

Conclusions: Our cohort included older patients and those with impaired liver function. Although imAEs frequently occurred early after treatment initiation, they were manageable with appropriate clinical interventions.

Initial Experience with Nivolumab Plus Ipilimumab for Unresectable Hepatocellular Carcinoma, Including Predictions of Efficacy and Safety

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This study aimed to investigate the initial experience with nivolumab plus ipilimumab (Nivo/Ipi) for unresectable hepatocellular carcinoma. Eleven patients, including 4 patients of 1st line therapy, were treated with Nivo/Ipi. Outpatient follow-ups were performed weekly. Tumor response based on RECISTv1.1 was an objective response rate of 36% and a disease control rate of 55%. Changes in AFP and DCP values at week 4 relative to the baseline showed significant differences between responders and non-responders ($p=0.016$ and $p=0.016$, respectively). In the responder group, a decrease in DCP was observed one week prior to the decrease in AFP. The incidence rate of severe irAEs (grade 3 or more) was 45.5%. The median pretreatment peripheral blood CD4+/8+ T cell ratio (CD4/8-R) was 1.22. A receiver operating characteristic curve showed that the optimal cutoff value for predicting severe irAEs was 1.195. Of the six patients with a CD4/8-R >1.195, four (67%) developed severe irAEs. In contrast, of the five patients with a CD4/8-R <1.195, only one patient (17%) developed severe irAEs. In conclusion, DCP could serve as a surrogate marker for very early response, and the pretreatment peripheral blood CD4+/8+ ratio may also serve as a predictive marker for the development of severe irAEs.

Effects and Side Effects for Unresectable Hepatocellular Carcinoma Treated by Atezolizumab plus Bevacizumab

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Background: For unresectable hepatocellular carcinoma in Japan, three combination therapies are available when immunotherapy is indicated, among these, five years have passed since our hospital initiated atezolizumab(Atezo) plus bevacizumab(Bev) combination therapy for hepatocellular carcinoma in November 2020, and the long-term prognosis is becoming clearer.

Methods: Twenty-five patients who started Atezo+Bev therapy at our hospital between October 2020 and December 2024. The observation period extended through December 2025. Treatment response was assessed every three cycles using contrast-enhanced CT or EOB-MRI based on mRECIST ver1.0. Adverse events were evaluated using CTCAE ver5.0.

Results: The 1-year survival rate after Atezo+Bev was 78.6%, and the 3-year survival rate was 43.7%. PFS was 49.3% at 1 year and 49.3% at 3 years. The best treatment response was CR in 7 cases (28%), PR in 8 cases (32%), SD in 2 cases (8%), and PD in 8 cases (32%). Of the 6 CR cases, Univariate analysis of factors associated with ORR (CR+PR) showed associations with DCP (<825) (P=0.041) and ALT (<21) (P=0.041). Multivariate analysis for survival-related factors identified Child-Pugh score 5 (A) (P=0.0016) and ORR cases (P=0.0084). Adverse events occurred in 13 patients (52%), with grade 3 events in 11 patients (44%).

Conclusion: Atezo plus Bev therapy demonstrated favorable treatment efficacy, with some CR cases showing long-term survival. Treatment initiation at Child-Pugh A score five should be considered, and ORR cases were found to have a favorable prognosis. Management of grade 3 irAE side effects were deemed critical.

Efficacy and Safety of Atezolizumab plus Bevacizumab in Advanced Hepatocellular Carcinoma with Child-Pugh Class B: A Single-Center Study

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Background: Although chemotherapy with atezolizumab plus bevacizumab is recommended for advanced hepatocellular carcinoma in patients with Child-Pugh (CP) Class A, there is limited data regarding the efficacy and safety in advanced hepatocellular carcinoma with CP B.

Methods: In this retrospective study, we enrolled 72 consecutive patients (59 patients with CP A and 13 patients with CP B) who received chemotherapy with atezolizumab plus bevacizumab at our institution from October 2020 to May 2025. The objective response rate (ORR), the disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and adverse events were evaluated.

Results: 28 patients (38.9%) and 44 patients (61.1%) were classified as BCLC stage B and C, respectively. 59 patients (81.9%) received the chemotherapy in the first-line setting.

In CP A and B patients, the ORR was 35.6% and 38.4% (P=1.00), and the DCR was 88.1% and 61.5% (P=0.03). The median OS was 8.0 months in CP B, compared to 17.7 months in CP A (P=0.30), and the median PFS was 4.4 months in CP B, compared to 9.3 months in CP A (P=0.22). Grade 3 or higher adverse events occurred in 22.0% and 15.4% of CP A and B patients (P=0.72), respectively.

Conclusion: In advanced hepatocellular carcinoma with CP B, compared to CP A, there were no significant differences in ORR or the proportion of severe adverse events; however, OS and PFS tended to be shorter. This study included a small number of cases, and multicenter studies are needed in the future.

Efficacy of Immunotherapy for Hepatocellular Carcinoma in the Elderly

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Objective: To clarify the efficacy of immunotherapy (IO) for elderly patients over 75yo (Over) patients with hepatocellular carcinoma (HCC), specifically comparing the combination therapy of Atezolizumab+Bevacizumab (Ate+Bev) and Durvalumab+Tremelimumab (Dur+Tre).

Methods: The study included 116 cases treated with Ate+Bev and 19 cases treated with Dur+Tre at our department. Overall survival (OS) was compared from the start date of IO treatment, and comparisons were also made between advanced-aged and non-advanced-aged patients.

Results: Among over 75yo patients, 5 cases received Dur+Tre. For Ate+Bev, 58 cases were included. (1) Comparison between Dur+Tre and Ate+Bev: No significant difference was observed in the mean OS after the start of treatment (Ate+Bev/Dur+Tre = 927/950 days). (2) Comparison of Dur+Tre between Over and under 75yo patients (Under): No significant difference was observed in mean OS, although there was a tendency for shorter OS in Over compared to Under (Over/Under = 604/1069 days). (3) Comparison of Ate+Bev combination therapy between Over and Under: No significant difference was observed in mean OS (Over/Under = 872/964 days). (4) Analysis of Dur+Tre combination therapy in Over: Blood tests, biochemical tests, and tumor markers before treatment and at 4 weeks after treatment were compared between Over and Under. No significant differences were found in any parameters. In addition, no significant differences were observed in any parameters before and after treatment in Over.

Conclusion: Dur+Tre treatment, over 75yo patients may not achieve the same extension of prognosis as under 75yo patients, indicating the need for further investigation.

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Bevacizumab only Treatment Outcomes After Invasive Treatment of HCC Classified by Hepatitis Virus Type, Gender, and Age Group

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Bevacizumab (Avastin), a vascular endothelial growth factor (VEGF) inhibitor, is widely used in targeted therapy for advanced HCC. This study compared Bevacizumab treatment outcomes measured by the number of treatment courses, reflecting long-term tolerance and treatment duration across viral infection types, gender, and age groups. Data were extracted from medical records of 559 HCC patients treated with Bevacizumab at Interferon Alpha Hospital during 2023 to 2025.

Methods: Age, gender, viral status, and number of treatment courses were collected from 559 patients. Average number of courses was calculated for each subgroup. Survival was assessed by a phone call.

Results: Among 559 patients, the overall average number of Bevacizumab courses was 7.13 (range 1 to 19). Males (n=346) had a slightly higher average (7.53 courses) than females (n=213, 7.16 courses). Mean age was 58.4 years (range 36 to 75). 2-year survival rate was 68.6% (n=384). By gender: Males demonstrated marginally better outcomes than females, though the difference was small. By age group: Patients aged more than 60 years had the highest average number of courses, while those younger than 50 years had the lowest. The correlation between age and number of courses was moderately positive (r=0.43).

Conclusion: Bevacizumab treatment tolerance and duration were highest in patients with HCV-only infection, males, and those over 60 years of age. 2-year survival rate was 68.6% which is much higher than patients without Bevacizumab which was 30-50%. We consider our results comparable to well developed countries of Asia.

A Pretreatment Serum Cytokine Score Predicts Response to First-line Atezolizumab/Bevacizumab in Unresectable Hepatocellular Carcinoma

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Background: Although atezolizumab plus bevacizumab (Atezo/Bev) is widely used as first-line therapy for unresectable hepatocellular carcinoma (HCC), clinically practical biomarkers to predict benefit remain limited.

Methods: We retrospectively analyzed 75 patients who initiated first-line Atezo/Bev between October 2020 and December 2023. Pretreatment stored serum was profiled using the Bio-Plex Pro Human Cytokine GI 27-plex panel. Treatment response was assessed by RECIST v1.1 (best response). Cytokines associated with objective response were screened using the Mann-Whitney U test ($p < 0.05$). Selected cytokines were dichotomized at the cohort median (low=0, high=1) and summed to generate a 0-5 cytokine score. Predictive performance was evaluated by ROC analysis, and the optimal cut-off was explored using the Youden index.

Results: Median overall survival was 19.6 months, and median progression-free survival was 6.6 months. Five cytokines were associated with objective response: G-CSF, IL-6, IL-8, IP-10, and MIP-1 α (all $p < 0.05$). Overall objective response rate was 26/75 (34.7%). Objective response rates by score were 56.3% (9/16), 40.0% (4/10), 45.5% (5/11), 30.8% (4/13), 15.4% (2/13), and 16.7% (2/12) for scores 0-5, respectively. The 5-cytokine score showed modest discrimination for objective response (AUC=0.686).

Conclusions: A pretreatment serum cytokine score integrating G-CSF, IL-6, IL-8, IP-10, and MIP-1 α may help predict objective response to first-line Atezo/Bev in unresectable HCC. External validation is warranted.

Predictive Factors for Response to Dual Immune Checkpoint Inhibitor Therapy in Advanced Hepatocellular Carcinoma

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Background: Dual immune checkpoint inhibitor (ICI) therapy is a key treatment for advanced hepatocellular carcinoma (HCC), yet individual responses vary significantly. While useful predictive factors such as FDG-PET/CT and the CD4/CD8 ratio (CD4/8-R) have been reported for durvalumab plus tremelimumab (Dur/Tre), effective predictors for nivolumab plus ipilimumab (Nivo/Ipi) remain undefined. We evaluated the utility of these markers across both regimens.

Methods: From July 2023 to November 2024, we analyzed 8 patients with advanced HCC who underwent FDG-PET/CT and peripheral blood CD4/8-R measurement before initiating Dur/Tre or Nivo/Ipi. Treatment response was assessed using RECIST version 1.1. PET positivity was defined as a tumor-to-normal liver ratio (TLR) > 2.0 .

Results: The cohort included 4 Dur/Tre and 4 Nivo/Ipi cases. Overall median age was 72 years; 7 patients were Child-Pugh class A. In the Dur/Tre group (3 PET-positive, median CD4/8-R: 1.9), outcomes included 1 partial response (PR) (PET-positive, CD4/8-R: 4.9) and 1 stable disease (SD) (PET-positive, CD4/8-R: 1.2). In the Nivo/Ipi group (1 PET-positive, median CD4/8-R: 1.0), 2 patients achieved SD despite being PET-negative with low CD4/8-R (0.9 and 1.0).

Conclusions: Our findings align with previous reports that PET positivity and high CD4/8-R predict response to Dur/Tre. Conversely, Nivo/Ipi may demonstrate efficacy even in PET-negative cases with low CD4/8-R, suggesting that predictive cutoff values may need to be regimen-specific. Further large-scale validation is required.

Evaluation of Liver and Spleen Volume Changes during Systemic Therapy for Hepatocellular Carcinoma

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Background: Liver and spleen volume changes are observed in some cases during systemic therapy for hepatocellular carcinoma (HCC).

Methods: Among 120 patients who received systemic therapy for HCC between 2014 and 2024, 11 patients who continued the same regimen for at least 6 months and had analyzable 1-mm-slice contrast-enhanced CT data were included. Spleen volume was assessed in all patients except one who had undergone splenectomy. Liver and spleen volumes at treatment initiation and at 6 months were measured using a 3D image analysis system (SYNAPSE VINCENT; Fujifilm Medical).

Results: The mean age was 67.4 ± 10.3 years; 7 patients were male. BCLC stage was B in 1 patient and C in 10 patients. Treatment regimens included regorafenib (n=3), lenvatinib (n=5), and atezolizumab plus bevacizumab (n=3), administered as first-line (n=5), second-line (n=4), or third-line (n=2) therapy. At 6 months, treatment response was partial response in 2 patients, stable disease in 4, and progressive disease in 5. A $\geq 15\%$ decrease in liver volume was observed in 66.7% of patients treated with regorafenib, 60.0% with lenvatinib, and none with atezolizumab plus bevacizumab. A $\geq 10\%$ increase in spleen volume was observed in 33.3% of patients treated with regorafenib and in all patients treated with atezolizumab plus bevacizumab.

Conclusion: During systemic therapy for HCC, regorafenib and lenvatinib tend to be associated with liver volume reduction, whereas atezolizumab plus bevacizumab tends to be associated with spleen volume increase.

Effects of Combination Therapy with Tremelimumab and Durvalumab on Skeletal Muscle Mass and Cardiac Function in Patients with Unresectable Hepatocellular Carcinoma

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Background: We previously reported that anti-VEGF agents such as sorafenib and lenvatinib reduce skeletal muscle volume (SMV) through impaired carnitine absorption in patients with hepatocellular carcinoma (HCC). In addition, bevacizumab was shown to reduce SMV and cardiac function (CF) in elderly patients, independent of carnitine metabolism. However, the effects of immunotherapy on SMV and CF remain unclear.

Objective: To investigate effects of therapy with tremelimumab and durvalumab (Tre/Dur) on SMV and CF in patients with HCC.

Methods: Nineteen patients with HCC were received Tre/Dur therapy at our hospital. Blood samples were collected before treatment and at 4 weeks treatment to measure serum levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Abdominal CT scans were performed at 8 weeks treatment to evaluate therapeutic response according to mRECIST and to calculate the psoas muscle index (PMI) based on the cross-sectional area of the psoas muscle. In addition, CF was assessed using global longitudinal strain (GLS) on transthoracic echocardiography.

Results: The study included 11 male and 8 female patients, all of whom had cirrhotic livers. Treatment responses were as follows: PR in 3 patients, SD in 8, and PD in 8. Serum GH and IGF-1 levels showed a significant increase at 4 weeks after treatment. However, PMI values significantly decreased at 8 weeks. There was no significant change in GLS at 4 weeks, indicating that left ventricular systolic function remained stable.

Conclusion: Tre/Dur combination therapy for HCC does not adversely affect cardiac function but is associated with a reduction in SMV.

Intratumoral Vascular Lake Formation in Patients with Hepatocellular Carcinoma treated with Atezolizumab plus Bevacizumab or Lenvatinib

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Background: Intratumoral vascular lake formation is a complication observed during treatment with atezolizumab plus bevacizumab (Atezo+Bev) or lenvatinib (LEN) in patients with hepatocellular carcinoma (HCC). This study aimed to investigate the risk factors, subsequent management, and clinical outcomes associated with this complication.

Methods: Among 207 patients who received Atezo+Bev or LEN as first-line therapy at our institution between June 2013 and September 2025, the presence of intratumoral vascular lakes on contrast-enhanced imaging was retrospectively evaluated. Potential risk factors, including tumor size, laboratory parameters, and baseline clinical factors associated with the development of vascular lakes were analyzed using univariable logistic regression. Subsequent clinical courses were also examined.

Results: Intratumoral vascular lakes developed in 7 (4 with Atezo+Bev and 3 with LEN) patients (3.4%). A tumor diameter of ≥ 50 mm (odds ratio [OR] 5.91, $p = 0.017$) and an AFP level ≥ 100 ng/mL (OR 4.35, $p = 0.047$) were identified as risk factors. Intratumoral vascular lakes were incidentally detected on scheduled imaging in 2 patients and following HCC rupture in 5 patients. Transarterial embolization (TAE) was performed in 6 patients, all of whom achieved hemostasis. However, one patient died from massive intraperitoneal hemorrhage before TAE could be performed. After achieving hemostasis, systemic therapy was resumed for 4 patients, while the remaining 2 patients were transitioned to best supportive care.

Conclusions: Larger tumor size was identified as a risk factor for intratumoral vascular lake formation. Although most cases were successfully managed with TAE, this complication may occasionally result in serious clinical outcomes.

Outcomes of Locoregional Therapy Followed by Combination Immunotherapy for Unresectable Hepatocellular Carcinoma

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Background: Combining locoregional therapy (LRT) with immunotherapy-based systemic therapy (ST) is an emerging strategy for unresectable hepatocellular carcinoma (uHCC). Although multiple phase III trials have demonstrated progression-free survival (PFS) benefit with combined approaches, the optimal sequencing and choice of LRT and ST remain undefined.

Methods: We retrospectively evaluated patients with uHCC who received LRT within 3 months before initiation of immunotherapy-based ST between 2020 and 2024. Outcomes were assessed at the patient level.

Results: Twelve episodes meeting the inclusion criteria were observed in 11 patients. Median age was 76 years, and 91% were male. BCLC stage was B in five patients and C in six. LRT consisted primarily of transarterial chemoembolization (TACE; n = 9). Selected immunotherapy-based ST before LRT was atezolizumab plus bevacizumab (AB) in seven patients, durvalumab plus tremelimumab (DT) in four, and durvalumab in one. The overall response rate was 25%, including two complete responses. Median PFS was 146 days. Five patients achieved prolonged PFS exceeding 500 days; all had prior TACE exposure and received AB. Three long-term responders initially received DT after LRT and transitioned to AB before disease progression, including two who underwent AB rechallenge. On-demand TACE was performed in three long-term responders.

Conclusions: Outcomes following LRT combined with immunotherapy-based ST were heterogeneous. Prolonged disease control was observed predominantly in patients with prior TACE exposure who received AB, suggesting a potential interaction between TACE and anti-VEGF-containing immunotherapy regimens. Add-on TACE and DT followed immediately by AB may warrant further research in this population.

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Continuing or Switching Systemic Therapy Combined with Locoregional Therapy Defines a Personalized Strategy for Oligoprogression in Hepatocellular Carcinoma: A Multicenter Retrospective Study

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Background: The optimal management of oligoprogression during first-line immune checkpoint inhibitor-based therapy for advanced hepatocellular carcinoma (HCC) remains unclear. This study compared the outcomes between continuing first-line systemic therapy combined with locoregional therapy (FLST+LRT), switching to second-line systemic therapy combined with LRT (SLST+LRT), or switching to SLST alone.

Methods: This multicenter, retrospective study enrolled 226 patients with oligoprogressive HCC. Patients were stratified into FLST+LRT (n = 87), SLST+LRT (n = 93), and SLST alone (n = 46) groups. Overall survival (OS) and progression-free survival were analyzed. Factors associated with overall were identified.

Results: Median OS was significantly longer in both FLST+LRT (26.4 months) and SLST+LRT (24.9 months) groups compared to SLST alone (18.1 months; p = 0.041 and p = 0.029, respectively). Subgroup analyses demonstrated that among durable responders, FLST+LRT achieved a median OS of 42.5 months, superior to SLST+LRT (19.1 months, p = 0.049) and SLST alone (18.3 months, p = 0.006). In non-durable responders, SLST+LRT resulted in longer median OS than both FLST+LRT (p = 0.030) and SLST alone (p = 0.042). For intrahepatic progression, both LRT-based strategies improved OS compared to SLST alone (p = 0.004 and p < 0.001, respectively). Multivariate analysis identified ALBI grade (hazard ratio [HR] 1.846, p = 0.013), no LRT after oligoprogression (HR 1.683, p = 0.040) and AFP > 200 ng/mL (HR 1.795, p = 0.012) as independent prognostic factors for OS.

Conclusions: Integrating locoregional therapy for oligoprogressive HCC significantly improves survival compared to switching systemic therapy alone. Treatment should be individualized based on the prior response duration and progression pattern.

Clinical Outcomes of TACE/TAI using Cisplatin Combined with Lenvatinib as Second-line Therapy After Failure or Intolerance to Immune Checkpoint Inhibitors

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Purpose: This study aimed to evaluate the clinical outcomes of transarterial chemoembolization (TACE) or transarterial infusion (TAI) using cisplatin combined with lenvatinib as second-line therapy following ICI failure or intolerance.

Methods: We retrospectively analyzed 10 patients who underwent hepatic arterial therapy using cisplatin combined with lenvatinib after failure or intolerance to ICIs between February 2019 and August 2025. The median age was 65 years (range: 31-79), with 9 males and 1 female. Liver function was Child-Pugh class A in 8 patients and class B in 2 patients. According to the BCLC staging system, 2 patients were stage B (Up-to-7-11: n=1; beyond Up-to-11: n=1) and 8 were stage C (macrovascular invasion: n=3; extrahepatic spread: n=5). All patients received this combination therapy as second-line treatment. Prior ICI regimens included atezolizumab plus bevacizumab (n=5), durvalumab plus tremelimumab (n=4), and other regimens (n=1). Seven patients underwent TACE (HepaSphere: n=6; lipiodol: n=1) using cisplatin, and three underwent TAI.

Results: Tumor response included partial response (PR) in 6 patients (TACE: 4; TAI: 2), stable disease (SD) in 1 patient (TACE: 1), and progressive disease (PD) in 3 patients (TACE: 2; TAI: 1), yielding an overall response rate (ORR) of 70%. Grade ≥ 3 adverse events included elevations in AST/ALT (n=2), biliary stricture (n=1), hand-foot syndrome (n=1), and proteinuria (n=1).

Conclusion: TAI or TACE using cisplatin combined with lenvatinib demonstrates acceptable and promising clinical outcomes as second-line therapy after failure or intolerance to immune checkpoint inhibitors in patients with advanced HCC.

Two Cases of Unresectable Hepatocellular Carcinoma Treated with LEN-TACE for Local Control during Dual Immune Checkpoint Inhibitor Therapy

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Introduction: In Japan, several combination immunotherapies are available for unresectable hepatocellular carcinoma (HCC), including Atezolizumab/Bevacizumab (Atezo/Bev), Durvalumab/Tremelimumab (STRIDE), and Nivolumab/Ipilimumab (Nivo/Ipi). We report two cases highlighting the integration of locoregional therapy with immune checkpoint inhibitor combinations.

Case presentation: Case 1: A male in his 70s with extrahepatic metastases (BCLC C) received Nivo/Ipi as third-line therapy. Baseline liver function was Child-Pugh A (6 points), mALBI grade 2b. At 8 weeks, imaging showed a partial response in extrahepatic lesions, but the sole intrahepatic lesion progressed with an elevation of tumor markers. LEN-TACE was performed for local control, resulting in marked improvement in tumor markers, and Nivo/Ipi was continued. Case 2: An 80s male with multiple HCCs (BCLC B, up to 11 out) started STRIDE as first-line therapy. Baseline liver function was Child-Pugh A (6 points), mALBI 2b. After 8 weeks, most intrahepatic lesions regressed, except for one in segment 8, which progressed with contrast enhancement of the tumor. LEN-TACE was performed for local control, leading to decreased tumor markers, and STRIDE was continued.

Discussion: In both cases, local progression showing arterial enhancement was controlled with LEN-TACE, enabling continuation of systemic therapy. While locoregional therapy combined with Atezo/Bev is reported to improve prognosis, evidence for such combinations with IO/IO regimens remains limited. We discuss these cases with a brief literature review.

The Evaluation of Clinical Impact of Additional TACE to Lenvatinib for HCC Patients

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Background: We have experienced the advantage of additional TACE to systemic chemotherapy for controlling intrahepatic lesions. Here, we evaluate the effect of additional TACE to Lenvatinib (LEN). **Methods:** HCC patients treated with LEN from 2018 May to 2025 May at our institute were enrolled. Totally seventy-six patients were categorized into scheduled LEN-TACE (N=12), LEN-on demand TACE (N=35), and LEN monotherapy (N=29). The median PFS and OS were compared to evaluate the appropriate candidates for additional TACE.

Results: In BCLC-B, scheduled LEN-TACE (N=11) tended to be worse hepatic reserve ($p<0.05$) and less proportion with previous systemic chemotherapy ($p=0.07$) compared to LEN-on demand TACE (N=18) and LEN monotherapy (N=15) groups. The periods (days) of median OS/PFS of each group were not reached/not reached, 1207/238, and 368/122, respectively. Both OS and PFS of LEN monotherapy were significantly shorter compared to other groups ($p<0.01$). Furthermore, by evaluating with up-to-11 status, the same phenomena were observed. On the other hand, patients with BCLC-C, LEN-on demand TACE (N=17) tended to be older ($p<0.05$) compared to LEN monotherapy (N=14), whereas there were no other significant differences in other patient's characteristics. The periods (days) of median OS/PFS of each group were 744/257, and 314/175, showing that additional TACE provides significantly longer PFS than LEN monotherapy ($p<0.05$).

Conclusion: Among BCLC-B HCC patients, additional TACE to LEN provided significant longer PFS and OS compared to LEN monotherapy. In terms of the tumor burden, up-to-11 in status is particularly efficacious factor to undergo TACE with LEN for achieving better clinical outcome.

The Impact of Scheduled LEN-TACE on Tumor Microenvironment for BCLC-B HCC

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Background: The BCLC-B HCC group constitutes a very heterogeneous patient population. In TACTICS-L trial, scheduled Lenvatinib (LEN) with TACE (LEN-TACE) has shown promising efficacy even in TACE-unsuitable patient groups. Although TACTICS-L trial enrolled Child-Pugh classification A, we often encounter cases with impaired hepatic reserve capacity. Therefore, the efficacy of scheduled LEN-TACE in the clinical practice was evaluated.

Methods: 11 HCC patients treated with scheduled LEN-TACE at our institute were enrolled. In recent 4 cases, blood samples were collected 1) before treatment, 2) 1week after the LEN therapy, 3) 1week after TACE, and 4) 1week after reinitiation of LEN. The concentrations of sera Ang-2 were measured with ELISA kit and peripheral PBMC was analyzed with FACS to evaluate the proportion of effector Treg as CD4+CD45RA-FOXP3+ cells.

Results: In 10 patients out of 11 patients, the status of up to 7 criteria was within. In terms of the best response, ORR ratio was 90.9% (10/11) because CR and PR were achieved in 7 and 3 patients, respectively. Even among the patients with non-single nodular type or mALBI 2b, ORR ratios were 87.5% (7/8) or 85.7% (6/7), respectively. During the scheduled LEN-TACE therapy, the concentrations of Ang-2 were significantly decreased after the administration of LEN and the proportion of effector Treg in PBMC was decreased.

Conclusion: Scheduled LEN-TACE provides high therapeutic efficacy even in the patients categorized as TACE-unsuitable group. From the viewpoints of tumor microenvironment, LEN-TACE could contribute to ideal change for cancer immunity by reducing the proportion of peripheral effector Treg.

Lenvatinib plus Drug-eluting Bead Transarterial Chemoembolization for Large Hepatocellular Carcinoma beyond the Up to 7 Criteria

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Aims: To evaluate the efficacy and safety of lenvatinib combined with drug-eluting bead transarterial chemoembolization (LEN-DEB TACE) for large HCC beyond the up-to-7 criteria and to identify prognostic factors.

Methods: Between November 2022 and September 2025, 15 patients with HCC (>6 cm) were retrospectively analyzed. Lenvatinib was administered for 4 days before TACE, followed by DEB TACE using epirubicin-loaded DC Beads. Additional cTACE was performed later in cases with residual viable tumor. After TACE, lenvatinib was restarted at a reduced dose and adjusted as clinically indicated. Tumor response, progression free survival (PFS), TACE specific PFS, and overall survival (OS) were evaluated. Prognostic factors were analyzed using the Cox proportional hazards model.

Results: The objective response rate (CR+PR) was 93.3%, including 80.0% CR rate. Median PFS was 6 months (95%CI, 0.0-13.1), with a 1 year PFS rate of 39.6%. Median TACE specific PFS was not reached, and the 1 year rate was 66.0%. Median OS was 26 months (95%CI, 17.5-35.0), with a 1 year OS rate of 71.0%. Post TACE lenvatinib relative dose intensity (RDI; median 46.7%) showed a trend toward improved PFS (HR, 0.87; 95%CI, 0.73-1.03). The high RDI group demonstrated longer PFS than the low RDI group (17 vs. 2 months, $p=0.048$). Grade>3 adverse events included AST/ALT elevation (30.8%) and acute kidney injury related to tumor lysis syndrome (15.4%), all managed conservatively.

Conclusions: LEN-DEB TACE achieved a high response rate in large HCC beyond the up-to-7 criteria. Continuation of lenvatinib after TACE may be crucial for prolonging PFS.

Toxicity Turned Tolerance: Hematologic Adverse Events Managed Successfully in Hepatocellular Carcinoma with VP4 Portal Vein Tumor Thrombus Under Atezolizumab-Bevacizumab: A Case Report from Vietnam

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Background: Atezolizumab plus bevacizumab is the standard first-line therapy for unresectable hepatocellular carcinoma (HCC). Although uncommon, hematologic toxicities can be clinically significant, with thrombocytopenia (10.6%) and leukopenia (4-5%) reported in IMbrave150 trial. Given the limited guidance on management, we present a case highlighting safe mitigation of hematologic toxicity while preserving treatment efficacy

Case Presentation: A 45-year-old woman was diagnosed with BCLC C hepatocellular carcinoma with portal vein tumor thrombus (VP4) on a background of HBV-related cirrhosis, Child-Pugh A (5 points), confirmed by liver biopsy. Baseline: tumor 31 mm; AFP 272 ng/mL; platelets $151 \times 10^9/L$; ANC $5.4 \times 10^9/L$. She initiated treatment with atezolizumab-bevacizumab. After eight cycles, CT showed disappearance of the intrahepatic lesion and reduction in PVTT size with normalization of AFP, consistent with a partial response. After 10 cycles, platelets declined to $70 \times 10^9/L$ while cirrhosis remained stable, supporting bevacizumab-related thrombocytopenia. Bevacizumab was discontinued and atezolizumab continued every 3 weeks; platelet counts recovered and stabilized more than $100 \times 10^9/L$ after the first monotherapy cycle. During monotherapy, neutropenia (ANC $1.3 \times 10^9/L$) with fatigue emerged; the dosing interval was extended to every 4 weeks, with hematologic improvement and symptom resolution. After two years of sustained disease control, therapy was discontinued; the patient remains clinically, biochemically, and radiologically stable under active surveillance.

Conclusion: Bevacizumab discontinuation and atezolizumab interval extension corrected hematologic toxicity and maintained disease control, enabling planned treatment discontinuation with continued stability.

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Efficacy and Safety of Lenvatinib for Unresectable Hepatocellular Carcinoma in Patients with Severe Renal Impairment

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Background: Systemic therapy for unresectable hepatocellular carcinoma (uHCC) has rapidly advanced; however, with the aging population, the number of patients with concomitant renal impairment is increasing. Even in the era of immunotherapy, lenvatinib remains a potential therapeutic option for HCC patients with renal impairment.

Aim: To evaluate the efficacy and safety of lenvatinib in patients with uHCC complicated by severe renal impairment.

Patients and Methods: Between November 2020 and May 2024, six patients with uHCC and severe renal impairment (eGFR $<30 \text{ mL/min/1.73 m}^2$) who received lenvatinib were retrospectively analyzed.

Results: The etiologies were hepatitis B in two patients, hepatitis C in three patients, and non-B non-C in one patient. Two patients were receiving hemodialysis. Child-Pugh class A, B, and C were observed in 2, 4, and 0 patients, respectively, and BCLC stage A, B, and C in 0, 4, and 2 patients, respectively. Median AFP was 41.5 ng/mL (range: 93-2978), and median DCP was 320 mAU/mL (range: 112-49,125). All patients initiated lenvatinib at a dose of 4 mg/day. Overall survival rates at 6, 12, and 18 months were 66.7%, 50.0%, and 25.0%, respectively, with a median OS of 10.9 months (95% CI: 3.03-NA). Initial tumor response assessed by RECIST1.1 showed PR in 1 patient, SD in 2, PD in 2, and no CR. Adverse events included hepatic dysfunction, hand-foot skin reaction, anorexia, fatigue, worsening renal function, and proteinuria.

Conclusion: Lenvatinib appears to be a relatively safe and effective therapeutic option for patients with uHCC complicated by severe renal impairment.

A Super-Elderly Male with Multiple Hepatocellular Carcinoma Achieving Long-Term Survival by Repeated Percutaneous Ablation Combined with Lenvatinib

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Background: Recent advances in systemic therapy have expanded treatment options for patients with intermediate-stage hepatocellular carcinoma (HCC). The combination of molecular targeted agents and percutaneous ablation may contribute to prolonged survival. However, evidence regarding this approach in super-elderly patients with multiple comorbidities remains limited. We report a super-elderly patient with recurrent HCC treated by percutaneous ablation combined with lenvatinib.

Case Presentation: An 88-year-old man with alcohol-related cirrhosis (Child-Pugh A) underwent anterior sectionectomy and partial S6 resection for HCC at the age of 81. He was accompanied by diabetes, hypertension, coronary artery disease with low heart function, and prostate cancer. Seven months later, he got multiple intrahepatic recurrences, which were treated sequentially with percutaneous ablation. Further, lenvatinib was initiated at 8 mg/day because of rapid multifocal recurrence with elevation of alpha-fetoprotein (AFP) to 8,507 ng/mL. Contrast-enhanced MRI images showed loss of arterial enhancement or shrinkage in most lesions; however, one lesion enlarged, and AFP further increased to 25,761 ng/mL. This lenvatinib-resistant lesion revealed moderately to poorly differentiated HCC by biopsy, and was treated with percutaneous ablation. AFP subsequently decreased to 98 ng/mL. Lenvatinib was discontinued following dose-reduction at the age of 86 due to pleural effusion and ascites. Thereafter, small recurrent lesions were repeatedly treated with percutaneous ablation. At the age of 88, the patient remains alive without recurrence.

Conclusion: Dose-adjusted lenvatinib combined with a minimally invasive percutaneous ablation may be an effective treatment for HCC even in a super-elderly patient with multiple comorbidities, who achieved nearly six years of survival.

STP5-4 10129

Desired Outcome of the STRIDE Regimen in an Advanced HCC Patient with Multiple Poor Prognostic Factors Outside HIMALAYA Trial Criteria: A Case Report

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Background: Advanced hepatocellular carcinoma (HCC) with severe cirrhosis presents significant clinical challenges. We report a case of BCLC stage C HCC involving poor prognostic factors outside the HIMALAYA trial criteria - including Child-Pugh B cirrhosis, thrombocytopenia, severe ascites and HBV/HCV co-infection - that achieved stable disease with the STRIDE regimen.

Case Presentation: A 53-year-old male with chronic HBV/HCV co-infection and alcohol abuse was diagnosed with BCLC stage B HCC, Child-Pugh A. After two sessions TACE and radiotherapy (54 Gy/18 Fr) to the hepatic lesion, the disease progressed to BCLC stage C with pulmonary metastasis. His liver function also worsened to Child-Pugh B (7 points), complicated by severe ascites and thrombocytopenia (50 to 60 x 10⁹/L). The STRIDE regimen was initiated: a single priming dose of tremelimumab (300 mg) plus durvalumab (1500 mg), followed by durvalumab every 4 weeks. After 8 months, the patient achieved stable disease. Serum alpha-fetoprotein levels decreased significantly from 737 ng/mL to 373 ng/mL. The only immune-related adverse event was grade 2 dermatitis, successfully managed with topical corticoids. The patient experienced four episodes of acute decompensation (hypoalbuminemia and worsening ascites, pleural effusion), these were managed with oral diuretics spironolactone/furosemide (100 mg/40 mg) and albumin, acid amin supplementation.

Conclusions: The STRIDE regimen demonstrated efficacy and an acceptable safety profile in an advanced HCC patient with complex comorbidities excluded from the HIMALAYA trial. This regimen may be an optimal therapeutic option for patients with a high bleeding risk where VEGF inhibitors are contraindicated.

Successful Transcatheter Aortic Valve Implantation Enabling Continuation of Systemic Chemotherapy in a Patient with Hepatocellular Carcinoma and Severe Aortic Stenosis: A Case Report

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Case Report: An 80-year-old man with cirrhosis due to metabolic dysfunction-associated steatohepatitis was diagnosed with hepatocellular carcinoma (HCC) in 2019. He had a history of ischemic heart disease requiring three percutaneous coronary interventions. In addition, mitral regurgitation, tricuspid regurgitation, aortic stenosis, and aortic regurgitation had been documented. For the HCC, the patient underwent four sessions of transcatheter arterial chemoembolization, two sessions of radiofrequency ablation, and one course of radiation therapy; however, local control was difficult to achieve. In February 2024, systemic therapy with tremelimumab and durvalumab was initiated. Four months later, new lesions were detected, and the treatment regimen was switched to four cycles of atezolizumab plus bevacizumab (Atez/Bev). Subsequently, he developed exertional dyspnea and presented for an unscheduled medical evaluation. Transthoracic echocardiography revealed progression to severe aortic stenosis. He was diagnosed with congestive heart failure. Bevacizumab, which has potential cardiotoxic effects, was discontinued, and atezolizumab monotherapy was continued for an additional four cycles. Despite dietary sodium restriction and the initiation of diuretics, symptomatic improvement was limited. The patient subsequently underwent transcatheter aortic valve implantation (TAVI). Following the procedure, the exertional dyspnea resolved, and brain natriuretic peptide (BNP) levels improved. After careful cardiovascular evaluation, Atez/Bev therapy resumed. To date, the patient has received 17 cycles of treatment and has maintained a partial response.

Discussion: In selected patients with an anticipated favorable oncological prognosis, TAVI in patients with severe heart failure may be considered a therapeutic option to allow the continuation of life-prolonging anticancer treatment.

Subconjunctival Hemorrhage and Corneal Graft Failure following Atezolizumab plus Bevacizumab Treatment for Hepatocellular Carcinoma: A Case Report

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Background: Immune checkpoint inhibitors (ICIs) have become the first-line treatment for unresectable hepatocellular carcinoma (HCC). However, ICIs are known to potentially trigger rejection in transplant recipients. While the risk in liver transplant recipients is well-documented, reports of rejection in corneal transplant cases are extremely rare. We report a case of HCC where atezolizumab plus bevacizumab (Atezo/Bev) led to corneal graft failure and subconjunctival hemorrhage.

Methods: A 75-year-old male with HCV-related HCC and a history of two corneal transplantations for bullous keratopathy was indicated for systemic therapy due to lymph node metastasis. Considering both the potential risk of graft rejection and the expected therapeutic efficacy, Atezo/Bev was initiated. Six days after the first dose, the patient developed acute right eye pain and was diagnosed with right subconjunctival hemorrhage and corneal graft failure.

Results: Two weeks after the diagnosis of graft failure, the patient underwent a successful corneal re-transplantation. With the use of topical steroids, no further rejection occurred. Regarding HCC, the patient transitioned to lenvatinib as second-line therapy, achieving stable disease. However, he eventually died of liver failure nine months after the initiation of Atezo/Bev.

Conclusions: This case demonstrates that Atezo/Bev can induce severe corneal graft rejection and subconjunctival hemorrhage. When administering ICIs to patients with a history of corneal transplantation, clinicians must carefully weigh the risks and benefits and maintain close collaboration with ophthalmologists.

Progressive Multifocal Leukoencephalopathy During Atezolizumab Plus Bevacizumab Therapy for Hepatocellular Carcinoma: A Case Report

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Background: Progressive multifocal leukoencephalopathy: PML is a rare demyelinating disorder of the central nervous system caused by reactivation of the JC virus, usually occurring in severely immunocompromised patients. While atezolizumab plus bevacizumab has become a standard first line therapy for advanced hepatocellular carcinoma: HCC, rare neurological complications remain poorly characterized.

Case Presentation: A 72 years old man with chronic hepatitis B related HCC BCLC stage C had received long term systemic therapy centered on atezolizumab plus bevacizumab since 2022, combined with locoregional treatments including transarterial chemoembolization and stereotactic body radiotherapy. Two weeks after the 26th course of atezolizumab plus bevacizumab, he developed rapidly progressive behavioral abnormalities and mild left sided hemiparesis. Brain magnetic resonance imaging revealed non enhancing T2 weighted and FLAIR hyperintense lesions involving the right frontal white matter, corpus callosum, and left frontal white matter. Cerebrospinal fluid analysis showed no pleocytosis or evidence of infection, however, JC virus DNA was detected at 2×10^5 copies / μ L, confirming the diagnosis of PML. Given the suspected drug association, atezolizumab plus bevacizumab was discontinued, and the patient was managed with close clinical observation.

Conclusion: This case highlights PML as a rare but serious neurological complication during long term atezolizumab plus bevacizumab therapy for HCC. Awareness of atypical neurological symptoms is essential for early recognition and appropriate management in patients receiving immunotherapy.

A Case of Hepatocellular Carcinoma with Rectal Fistula Induced by Lenvatinib in a Patient with Crohn's Disease

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Background: Lenvatinib is a standard molecular targeted therapy for hepatocellular carcinoma (HCC). However, its inhibition of vascular endothelial growth factor (VEGF) receptors can lead to serious adverse events, including gastrointestinal perforation. We report a case of rectal fistula during lenvatinib treatment in a patient with pre-existing Crohn's disease (CD).

Methods: A 60s male with a long history of CD presented with multiple HCC (cT3N0M0, Stage IIIA, Child-Pugh B). CD was managed with 5-ASA, azathioprine, metronidazole, and nutritional therapy. For HCC, after two sessions of transarterial embolization (TAE), lenvatinib was initiated.

Results: One month after starting lenvatinib, the patient developed abdominal pain and fever. Contrast-enhanced CT revealed a new rectal abscess and fistula. Lenvatinib was immediately discontinued. He was managed with intensive nutritional therapy and antibiotics (tazobactam/piperacillin), which led to the successful resolution of the abscess and fistula. Currently, HCC is being managed with TACE alone without further molecular targeted agents.

Conclusions: This case suggests that lenvatinib may exacerbate underlying inflammatory bowel disease or impair mucosal healing, leading to fistula formation. While lenvatinib is effective for HCC, we should exercise extreme caution and closely monitor gastrointestinal symptoms when administering VEGF inhibitors to patients with a history of Crohn's disease.

Stepwise Immune Re-Sensitization Induced by Short-Term VEGF Inhibition Enhances Antitumor Efficacy of Repeated Durvalumab Re-Challenge in Advanced Hepatocellular Carcinoma: A Case Report

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Background: The clinical benefit of immune checkpoint inhibitor (ICI) re-challenge after treatment failure remains unclear in hepatocellular carcinoma (HCC), particularly in patients showing primary resistance to initial ICI-based therapy. Emerging evidence suggests that vascular endothelial growth factor (VEGF) inhibition may modulate the tumor immune microenvironment and restore ICI sensitivity; however, clinical examples remain extremely limited.

Case: A man in his 70s with metabolic dysfunction associated steatohepatitis-related advanced HCC received atezolizumab plus bevacizumab as first-line therapy, achieving long-term stable disease. Upon progression, second-line durvalumab plus tremelimumab resulted in radiological progression with increasing tumor markers. Short-term VEGF-targeted therapies with lenvatinib and cabozantinib were subsequently administered but discontinued due to adverse events and disease progression. Durvalumab monotherapy was then reintroduced, leading to a marked reduction in alpha-fetoprotein (AFP) levels (2100 to 966 ng/mL at 8 weeks) and radiological stable disease lasting approximately 15 months. After further progression, short-term lenvatinib was re-administered, followed by durvalumab re-re-challenge. This resulted in a more rapid and pronounced AFP decline (13,633 to 436 ng/mL within 5 months) compared with the prior re-challenge. Transarterial chemoembolization was added for residual disease control, and the patient continues durvalumab monotherapy with sustained disease control.

Conclusions: This rare case suggests that short-term VEGF inhibition may induce stepwise immune re-sensitization, restoring and accelerating responsiveness to durvalumab despite prior ICI failure. Repeated ICI re-challenge following VEGF modulation may represent a feasible therapeutic strategy in selected patients with advanced HCC.

Exceptional Long-term Survival with Low-dose FP Regimen Hepatic Arterial Infusion Chemotherapy after Immune and TKI Failure in Advanced Hepatocellular Carcinoma: A Case Report from Vietnam

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Background: Treatment options for late-line advanced hepatocellular carcinoma (aHCC) remain undefined, with survival beyond the second line are generally modest. Evidence is scarce, while novel systemic therapies are costly and not always accessible. In contrast, hepatic arterial infusion chemotherapy (HAIC), particularly with low-dose FP regimen, has demonstrated antitumor efficacy Asian studies, yet long-term survival reports remain rare.

Case Representation: A 67-year-old man with chronic hepatitis B-related HCC was diagnosed radiologically according to AASLD criteria, showing a large hepatic mass (12×13 cm) with arterial phase hyperenhancement and portal venous washout on contrast-enhanced CT, Vp3 portal vein invasion and no extrahepatic spread. Baseline AFP was 9181 ng/mL, ECOG 0 and Child-Pugh A5. Patient received atezolizumab-bevacizumab and lenvatinib as first- and second-line therapies, both achieving stable disease for 8 and 6 months. Salvage HAIC with low-dose FP regimen was initiated (cisplatin 7mg/m² and 5-fluoruracil 170mg/m², day 1-5, every 2 weeks).

During follow-up, tumor size decreased progressively and continuously at each 4-cycle assessment. After 18 months of uninterrupted HAIC, the tumor has shrunk to 5.7×5.1cm, AFP reduced to 740 ng/mL. Liver function remained Child-Pugh A, with no significant toxicities. A single liver abscess resolved with antibiotics. Patient discontinued treatment by personal choice, and remarkably, remains alive over 3 years after HAIC, maintaining preserved hepatic and good quality of life.

Conclusion: HAIC with the low-dose FP regimen may serve as a salvage option for aHCC patients who have failed multiple systemic therapy and preserved liver function, offering the potential for durable tumor regression and long-term survival.

Evaluation of the Efficacy of Sequential Therapy with New FP and Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

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Background: In this study, we retrospectively evaluated the outcomes of sequential treatment in patients who received both New FP (HAIC regimen consisting of infusion of CDDP mixed with lipiodol followed by continuous infusion of 5-FU) and Atezo+Bev.

Methods: The study included 39 HCC patients who received Atezo+Bev at our institution. Among them, 9 patients who received New FP as first-line therapy followed by Atezo+Bev were classified as Group A, and 8 patients who received New FP after progression on Atezo+Bev were classified as Group B.

Results: In the overall cohort, CR was observed in 3 patients, PR in 9, SD in 15, PD in 11, yielding ORR of 32% and DCR of 71.0%. Group A: The outcomes of first-line New FP therapy were PR in 3 patients, SD in 5, with ORR of 38% and DCR of 100%. For second-line Atezo+Bev, CR was observed in 2 patients, PR in 2, SD in 2, and PD in 3, resulting in ORR of 44% and DCR of 67%. Group B: The outcomes of first-line Atezo+Bev were PR in 1 patient, SD in 5, and PD in 2, with ORR of 13% and DCR of 75.0%. For second-line New FP therapy, PR was observed in 2 patients, SD in 3, PD in 2, yielding ORR of 29% and DCR of 71%.

Conclusion: In this cohort, a certain degree of tumor reduction was achieved regardless of whether New FP or Atezo+Bev was administered first. However, favorable responses to Atezo+Bev were also observed after prior New FP therapy.

5-fluorouracil plus Cisplatin Versus Cisplatin in Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma: A Multicenter Randomized Controlled Trial

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Background: Hepatic arterial infusion chemotherapy (HAIC) has been a treatment option for advanced hepatocellular carcinoma (HCC); however, its optimal regimen remains unclear. We compared the efficacy and safety of a cisplatin (CDDP) regimen and a 5-fluorouracil plus cisplatin (FP) regimen.

Methods: This multicenter, randomized phase II trial (JRCTs041180176) enrolled patients with unresectable HCC who were unsuitable for locoregional treatments, had a Child-Pugh score ≤ 8 , an ECOG performance status ≤ 2 , and were intolerant of or refractory to systemic therapy. The primary endpoint was progression-free survival (PFS), and secondary endpoints included overall survival (OS), objective response rate (ORR), subsequent conversion therapy rate, and adverse events.

Results: Thirty-three patients were enrolled until April 2020. The main analysis was performed although the target number of events had not been reached because of poor accrual. Baseline characteristics did not differ significantly between groups. PFS was significantly longer in the FP group than in the CDDP group (median 5.00 vs. 1.38 months; stratified log-rank test, $P = 0.0023$). OS tended to be longer in the FP group (median, 9.53 vs. 5.69 months). The ORR was higher (41.2% vs. 18.8%), and subsequent conversion therapies were performed more frequently in the FP group (23.5% vs. 12.5%). Catheter-related adverse events were more frequently observed in the FP group (23.5% vs. 6.3%).

Conclusions: The FP regimen was associated with significantly prolonged PFS compared with the CDDP regimen. Further studies are warranted to clarify the positioning of HAIC in the era of immunotherapy.

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Near-Complete Response to Nivolumab+Ipilimumab in HCC With IVC Invasion: An Exceptional Outcome Beyond Trial Eligibility

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Background: Hepatocellular carcinoma (HCC) with inferior vena cava (IVC) invasion carries an extremely poor prognosis, and no robust evidence supports immunotherapy in this population. Nivolumab plus Ipilimumab (Nivo/Ipi) has shown benefit in selected advanced HCC, yet patients with macrovascular invasion were largely excluded from pivotal trials such as CheckMate-9DW.

Case: A 66-year-old woman with HCV-related cirrhosis (F4) achieved SVR but developed repeatedly recurrent HCC from 2017 onward. Despite multiple locoregional therapies, including RFA, TAE, TACE, PSE, BRTO, and PTO, the disease remained refractory. In 2021, recurrence was accompanied by a 1.5cm IVC tumor thrombus. With limited effective options and ineligibility for guideline-supported systemic therapies, Nivo/Ipi was initiated in August 2025. Four cycles were administered; however, therapy was interrupted when the patient developed severe endocrine immune-related adverse events, including fulminant type 1 diabetes mellitus leading to diabetic ketoacidosis and concomitant painless thyroiditis. Intensive multidisciplinary management enabled stabilization.

Results: Despite early cessation, contrast-enhanced CT demonstrated marked shrinkage and complete loss of enhancement of the IVC tumor thrombus. According to mRECIST, the response was classified as near-complete response (near-CR). Intrahepatic lesions also regressed, and no new lesions were observed.

Conclusion: This case represents a rare instance of near-CR induced by Nivo/Ipi in HCC with IVC invasion. Even after severe endocrine irAEs, coordinated multidisciplinary care preserved therapeutic benefits. Nivo/Ipi may offer an exceptional salvage option for selected patients with advanced HCC and macrovascular invasion.

Dramatic Complete Response to Atezolizumab Plus Bevacizumab in Advanced Hepatocellular Carcinoma with Massive Liver Involvement

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Background: Immune checkpoint inhibitor-based regimens are currently recommended for patients with advanced hepatocellular carcinoma (HCC); however, their efficacy and safety remain unclear in patients with extensive hepatic tumor involvement (>50% liver occupancy) and main portal vein tumor thrombosis (Vp4). Here, we report a successfully treated case of Vp4-positive HCC with >50% liver involvement using atezolizumab plus bevacizumab (Atez/Bev).

Case Presentation: A man in his 60s with alcoholic liver cirrhosis was referred to our hospital because of jaundice and impaired liver function. Laboratory findings revealed marked hyperbilirubinemia (T-Bil 3.9 mg/dL) and substantially elevated tumor markers (AFP 9,426 ng/mL, DCP 1,069 mAU/mL). Contrast-enhanced CT demonstrated HCC occupying approximately 70% of the liver, accompanied by main portal vein tumor thrombosis and multiple bilateral lung metastases. Based on radiological findings and tumor marker levels, the patient was diagnosed with unresectable advanced HCC associated with alcoholic chronic liver disease. Esophagogastroduodenoscopy revealed no esophageal varices. After thorough discussion, systemic therapy was initiated at the patient's strong request. After two cycles of Atez/Bev therapy, jaundice improved, lung metastases resolved on imaging, and marked tumor regression was observed. After four cycles, tumor markers normalized, and a complete response was achieved by RECIST without any immune-related adverse events. Six months after initiation of Atez/Bev therapy, the patient remains alive without disease progression.

Conclusion: Atez/Bev may represent an effective therapeutic option for selected patients with advanced HCC characterized by extensive liver involvement (>50%) and Vp4.

Selective Control of Pulmonary Metastases by Chemotherapy in Hepatitis C-related Hepatocellular Carcinoma: A Case Report

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Case Report: The patient is a man in his late 60s with hepatitis C cirrhosis resulting from blood transfusion during cardiac surgery in his childhood. The initial hepatocellular carcinoma (HCC) was treated with posterior segmentectomy. The second and third HCCs were treated via radiofrequency ablations, after 1.1 and 1.6 years, respectively. The third HCC recurred at the tumor periphery, and was resected by segment 5 subsegmentectomy at 2.7 years. Five years after the initial diagnosis, he developed recurring bilateral lung and the right ilium metastases, which were treated with radiation therapy. However, these lesions recurred. Atezolizumab plus Bevacizumab were initiated at 5.3 years, followed by switching to Lenvatinib Mesilate at 5.8 years. Genetic testing revealed high microsatellite instability, and Durvalumab plus Tremelimumab was initiated after 6.5 years. This regimen achieved good control of the lung metastases, however, the other metastases continued to progress. At 6.9 years, he underwent resection of a large intraabdominal disseminated tumor. At 7.1 years, a palliative radiation therapy was required for the right buttock. The patient's general condition gradually deteriorated, and he died of fatal hemoptysis at 7.3 years, despite the absence of radiographic lung metastases, in the presence of extensive non-pulmonary metastases.

Conclusions: This case highlights the heterogeneity of metastatic HCC. We report histopathological findings of the primary and metastatic lesions to explore differences in therapeutic responsiveness between pulmonary and the other metastases.

Dual Tumor Response to Sequential Immune Checkpoint Inhibitors in Synchronous HCC and ESCC: A Case Report

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Background: Synchronous hepatocellular carcinoma (HCC) and esophageal squamous cell carcinoma (ESCC) are uncommon and pose therapeutic challenges, particularly when both tumors are unresectable and exhibit distinct biological features. Immune checkpoint inhibitors (ICIs) have become a key treatment option for advanced HCC and ESCC, but evidence for dual tumor responses and optimal sequencing in synchronous disease remains limited.

Methods: We describe a case of multifocal unresectable HCC with synchronous superficial ESCC that was treated with sequential ICI therapy, and we retrospectively reviewed the clinical course as well as radiological, endoscopic, and serological responses.

Results: A 78-year-old man with alcoholic liver disease presented with multifocal HCC and a PD-L1 negative ESCC. Systemic therapy for HCC was prioritized. Atezolizumab plus bevacizumab achieved tumor shrinkage in both lesions, as demonstrated by dynamic computed tomography and upper endoscopy, together with concordant reductions in tumor markers, but treatment was discontinued after the onset of an acute cerebral infarction. The regimen was then switched to durvalumab plus tremelimumab, which induced further HCC regression and complete endoscopic disappearance of the ESCC without severe immune-related adverse events.

Conclusions: Sequential ICI therapy achieved durable control of both HCC and ESCC despite PD-L1 negativity in the esophageal lesion. This case raises the possibility that tumor-agnostic immune modulation and immune crosstalk between coexisting malignancies may enhance antitumor activity, and suggests that further accumulation of similar cases and exploratory studies on predictive biomarkers and treatment strategies are needed.

Recurrence After Achieving a Drug-Free State Following Response to Systemic Therapy in Hepatocellular Carcinoma: A Retrospective Case Series

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Background: Recent advances in systemic therapy for advanced hepatocellular carcinoma (HCC) have enabled deep responses, including complete response (CR) according to RECIST or modified RECIST (mRECIST). Consequently, some patients discontinue systemic therapy and achieve a so-called “drug-free” state. However, data regarding recurrence after treatment discontinuation remain limited.

Methods: Among 888 patients who received systemic therapy for HCC at our institution between 2009 and 2025, we retrospectively identified 15 patients who discontinued systemic therapy after achieving a response. Five patients who developed recurrence during follow-up were analyzed.

Results: All five patients achieved radiological CR and/or sustained normalization of tumor markers before treatment discontinuation. Recurrence occurred 6–14 months after achieving the drug-free state. Three patients developed intrahepatic recurrence alone, while two experienced recurrence involving extrahepatic lesions. At recurrence, re-initiation of systemic therapy was feasible in two patients, and local therapies were administered in two patients. One patient transitioned to best supportive care due to deterioration in performance status.

Conclusions: Recurrence can occur even after achieving a drug-free state following a favorable response to systemic therapy in HCC. Careful surveillance after treatment discontinuation is warranted, and further accumulation of cases is needed to clarify recurrence patterns and optimal management strategies after relapse.

An Analysis of Progression Patterns After Response to Atezolizumab/Bevacizumab in Unresectable Hepatocellular Carcinoma

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Background: Atezolizumab plus bevacizumab (Atez/Bev) is a standard systemic therapy for unresectable hepatocellular carcinoma, and a subset of patients achieves RECIST PR/CR. However, real-world data on progression patterns and prognostic factors after initial response remain limited.

Methods: We retrospectively reviewed patients treated with Atez/Bev at our institution between November 2020 and November 2022. Patients who achieved RECIST 1.1 PR or CR and subsequently met PD criteria were included (n=14). We analyzed baseline clinical and tumor factors, treatment response, progression patterns, and post-progression management.

Results: Best response was CR in 2 patients and PR in 12 patients. At baseline, macrovascular invasion (MVI) was present in 5 patients and extrahepatic metastasis (EHM) in 3 patients. Median time from treatment initiation to best response was 5.9 months (1.4-24.1), and median time from best response to PD was 7.8 months (2.0-17.8). Progression was intrahepatic-only in 12 patients (86%). In the remaining 2 patients (14%), PD was driven by extrahepatic lesion growth without intrahepatic progression. Post-progression management included systemic therapy (n=9), conversion surgery (n=1), and best supportive care (BSC) (n=4, 29%).

Conclusions: Among 14 patients who achieved PR/CR and subsequently progressed, 86% had intrahepatic-only progression. Post-progression management was diverse: 1 patient underwent successful conversion surgery, 9 received systemic therapy, and 4 (29%) transitioned to BSC due to clinical deterioration. Larger studies are needed to define optimal post-progression strategies, including criteria for locoregional therapy and surgical resectability in patients with intrahepatic-confined progression.

Real-World Outcomes and Characteristics of Responders in Advanced Hepatocellular Carcinoma Treated with Durvalumab/Tremelimumab

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Background: Durvalumab/Tremelimumab combination therapy (Dur/Tre) demonstrates efficacy in advanced hepatocellular carcinoma (HCC). However, concerns remain regarding the high incidence of immune-mediated adverse events (imAEs) in real-world practice. This study analyzes clinical data to evaluate treatment outcomes and characteristics of responders.

Methods: We retrospectively collected and analyzed clinical data from 96 patients with advanced HCC treated with Dur/Tre at Chiba University Hospital, Japan, from April 2023 to January 2025.

Results: Median age was 73 years. All patients had ECOG PS 0-1, and 82 patients (85.4%) had Child-Pugh A. Forty-eight patients (50.0%) received Dur/Tre as first-line treatment. Median progression-free survival was 4.4 months (95% CI: 3.1-4.9), and median overall survival was 20.4 months (95% CI: 14.9-29.1). Best overall response by RECIST criteria showed CR in 2 patients (2.1%), PR in 14 (14.6%), SD in 48 (50.0%), PD in 28 (29.2%), and NE in 4 (4.2%); mRECIST criteria showed CR in 5 patients (5.2%). ImAEs occurred in 54 patients (56.3%), with 36 patients (37.5%) requiring corticosteroid treatment. Among patients achieving RECIST CR or mRECIST CR, 3 had extrahepatic lesions only (all lymph node metastases) and 2 had intrahepatic lesions only (one with Vp4 invasion).

Conclusions: Dur/Tre frequently causes severe imAEs requiring corticosteroid treatment. Given the high toxicity, identification of responders is crucial to optimize patient selection for this therapy.

Real-World Early Experience with Ipilimumab Plus Nivolumab (IPINIVO) for Advanced Hepatocellular Carcinoma

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Background: The combination of ipilimumab plus nivolumab (IPINIVO) was approved for unresectable hepatocellular carcinoma (HCC) in 2025. We report our early clinical experience with IPINIVO and discuss treatment outcomes, safety, and management.

Methods: Eight patients with unresectable HCC who received IPINIVO were retrospectively analyzed. Patient characteristics, best overall response according to RECIST, and immune-related adverse events (irAEs) were evaluated.

Results: The median age of cases was 75 years. Non-viral etiology accounted for 75% of cases. All patients had Child Pugh class A liver function, with 63% classified as ALBI grade 1. Treatment lines included first-line therapy in 3 patients and fourth-line or later in 2 patients. BCLC stages B and C each accounted for 50%. Best overall response included partial response (PR) in 1 patient, yielding an overall response rate of 13% and a disease control rate of 63%. All patients ultimately discontinued treatment, and only one patient completed four planned cycles of IPINIVO. However, 63% were able to proceed to subsequent therapy, including those who discontinued due to irAEs. Severe irAEs were frequent; 88% of patients with grade 3-4 irAEs required high-dose corticosteroids, and one patient with steroid-refractory colitis required infliximab.

Conclusions: IPINIVO may provide meaningful clinical benefit even in advanced-stage HCC. However, early-onset and severe irAEs are common, underscoring the importance of close monitoring and intensive patient education to prevent delays in management of irAEs.

Lessons Learned from 1,716 Hepatobiliary Cancers: Real World Outcomes of Immune Checkpoint Inhibitor Therapy

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Objective: Our hospital initiated a cancer registry in 2006 based on predefined criteria and has conducted annual survival surveys in collaboration with local municipalities. Over the past 17 years, survival status has been ascertained for nearly all patients, encompassing 35,316 cases across 25 cancer types. Using this comprehensive real-world dataset, we aimed to evaluate the impact of immune checkpoint inhibitor (ICI) therapy on the treatment of hepatobiliary cancers.

Methods: Between October 2006 and December 2024, 608 patients with biliary tract cancer and 1,108 patients with hepatocellular carcinoma were registered. This analysis included 121 patients with unresectable advanced biliary tract cancer and 61 patients with unresectable advanced hepatocellular carcinoma.

Results: In biliary tract cancer, the median survival time (MST) was 10.8 months (95% CI, 4.7–17.0) in the ICI group (n=15) and 5.4 months (95% CI, 2.5–8.3) in the non-ICI group (n=106). In hepatocellular carcinoma, the MST was 49.5 months in the ICI group (n=10); confidence intervals could not be reliably estimated due to the limited number of events, whereas the MST was 3.3 months (95% CI, 1.9–4.7) in the non-ICI group (n=51).

Conclusion: Real-world data demonstrated improved survival outcomes with ICI therapy in both biliary tract cancer and hepatocellular carcinoma. Further analyses are warranted to identify factors associated with therapeutic benefit.

Exploring the Value of Imaging Indicators in Predicting TACE Refractoriness in Hepatocellular Carcinoma Based on Contrast-enhanced CT

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Background: To establish a predictive model for transarterial chemoembolization (TACE) refractoriness in unresectable hepatocellular carcinoma (HCC) based on tumor burden and radiomic features, and to assess its potential for early identification.

Methods: A retrospective cohort of 255 HCC patients treated with initial TACE between 2013 and 2024 at three Chinese centers was analyzed. Patients were divided into training (n = 110), internal testing (n = 47), and external testing (n = 98) cohorts. Logistic regression was used to construct a model from radiomic features extracted from preoperative arterial-phase CT, combined with clinical and semantic imaging predictors of TACE refractoriness after three cycles. Two additional TCGA cohorts (n = 70 and 40) were used for prognostic and biological validation.

Results: The combined model achieved AUCs of 0.85, 0.81, and 0.77 in training, internal, and external cohorts, respectively. Overall survival was significantly different between low- and high-risk groups across all datasets ($P < 0.05$). Transcriptomic analysis indicated that high-risk patients had upregulated genes and pathways linked to tumor aggressiveness and treatment resistance.

Conclusion: A biologically interpretable combined model was developed and externally validated to effectively predict post-TACE refractoriness in HCC, providing a robust tool for personalized therapeutic decision-making.

Trans Arterial Chemoembolization Combined with Immunotherapy for BCLC Stage B Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

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Background: Trans arterial chemoembolization (TACE) is the standard treatment for Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma (HCC), yet outcomes remain heterogeneous. Combination strategies incorporating immune checkpoint inhibitors (ICIs) may enhance treatment efficacy.

Methods: Databases were searched for comparative and single arm study evaluating TACE plus immunotherapy in BCLC stage B HCC. Outcomes included overall survival (OS), progression free survival (PFS), objective response rate (ORR), disease control rate (DCR), and grade >3 adverse event (AE). Pooled hazard ratio (HR) and risk ratio (RR) with 95% confidence interval (CI) were calculated using random effects models.

Results: Eleven studies were included qualitatively, and five contributed to quantitative synthesis. ICI used across studies included atezolizumab, pembrolizumab, Sintilimab, Camrelizumab, tislelizumab, Toripalimab, and PD-1 inhibitors combined with Lenvatinib or Sorafenib. Combination therapy significantly improved OS and PFS. ORR was higher with combination therapy using both RECIST and mRECIST. While DCR did not differ significantly. Qualitatively, both phase III and real-world studies consistently demonstrated improved tumour response and survival. Grade >3 AEs were more frequent with combination therapy, with low treatment-related mortality.

Conclusion: In BCLC stage B HCC, TACE combined with immunotherapy across multiple ICI platforms improves survival and tumour response, at the cost of increased but manageable toxicity.

Safety and Recurrence Patterns of Ablation After Immune Checkpoint Inhibitor Therapy for Hepatocellular Carcinoma

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Background: Ablation (ABL) after immune checkpoint inhibitor (ICI) therapy for hepatocellular carcinoma (HCC) is increasingly used for tumor eradication and potential immune-mediated systemic effects. However, real-world data on peri-procedural safety, inflammation, liver function changes, and recurrence patterns remain limited.

Methods: We retrospectively analyzed consecutive HCC patients who underwent ABL within 1 year of the last ICI dose at a single center. The primary outcome was 30-day complications by Society of Interventional Radiology (SIR) criteria. Secondary outcomes were inflammation (change in C-reactive protein [CRP] from baseline to postoperative day [POD] 7; duration of fever >38 C), liver function (ALBI at baseline, POD7, and POD28), and initial recurrence patterns.

Results: Among 213 ICI-treated patients, 14 (6.6%) underwent ABL: 13 after atezolizumab/bevacizumab and 1 after durvalumab (RFA n=12; MWA n=2). Median age was 78 years (IQR 75-85); all were male. One minor pneumothorax occurred and was managed conservatively; no major complications occurred. Median CRP increased by +3.28 mg/dL (IQR -0.28 to 11.89) at POD7. Median fever duration >38 C was 0 days (0/1/2 days in 11/2/1 patients). Median delta ALBI was +0.29 at POD7 and -0.01 at POD28, indicating transient worsening with recovery by 1 month. Two patients developed rapid multifocal intrahepatic progression originating near the ablation zone with peripheral spread; both had poorly differentiated HCC on biopsy.

Conclusion: ABL after ICI therapy was generally safe with limited inflammation and minimal impact on liver function. However, caution may be warranted for poorly differentiated HCC given a potential risk of aggressive post-ABL intrahepatic progression.

Clinical Response of Brain Metastasis from Hepatocellular Carcinoma Treated with a Multimodal Approach Using Lenvatinib and Radiotherapy: A Case Report

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Background: Brain metastasis from hepatocellular carcinoma (HCC) is rare and associated with poor prognosis. Optimal management of brain metastases from HCC remains undefined.

Methods: We report a case of advanced HCC with brain metastases managed using a multimodal approach incorporating lenvatinib and radiotherapy.

Results: A 42-year-old woman with chronic hepatitis B underwent hepatectomy for HCC in December 2023 and developed local recurrence in March 2024, which was treated with transarterial chemoembolization. In November 2024, she was referred to our department with headache and nausea. Brain magnetic resonance imaging revealed multiple brain metastases, with the largest lesion measuring 30 × 44 × 40 mm and causing a 12-mm midline shift. She was diagnosed with BCLC stage C HCC with brain and lung metastases and preserved liver function (Child-Pugh A, score 5). Despite intensive anti-edema therapy, her neurological condition rapidly deteriorated with decreased consciousness and quadriplegia. Lenvatinib was initiated at 8 mg/day, resulting in marked improvement in consciousness and muscle strength within one week. Lenvatinib was continued for one month before whole-brain radiotherapy (30 Gy in 10 fractions) was initiated to enhance intracranial disease control. After three months, imaging demonstrated a partial response (RECIST 1.1). The patient maintained a good quality of life, remained independent in self-care, and experienced no clinically significant adverse events. Disease control was maintained until November 2025. PFS and OS from lenvatinib initiation were 12 and 14 months, respectively.

Conclusions: Lenvatinib combined with radiotherapy may provide meaningful clinical benefit in selected patients with HCC and brain metastases. .

Hepatocellular Carcinoma with Submandibular and Sternal Manubrial Metastases: Tumor Growth Rate Based Dynamic Assessment and Regorafenib Combined with a Tonifying Eliminating Harmonizing Strategy

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Background: To report an advanced hepatocellular carcinoma case with metastases to the right submandibular soft tissue and manubrium, and to evaluate tumor growth rate (TGR) as a complement to RECIST 1.1.

Methods: Clinical data from November 2023 to September 2025 were retrospectively reviewed. TGR was estimated from serial CT measurements of the manubrial lesion at 2024-05-07, 2024-10-08, and 2025-05-09 using an ellipsoid surrogate based on orthogonal diameters. Findings were interpreted with RECIST 1.1, Child-Pugh, ALBI, MELD-Na, AFP, and DCP. Regorafenib was given at 80 mg once daily on days 1-21 every 28 days, then increased to 120 mg in May 2025. Traditional Chinese medicine decoctions were individualized.

Results: Biopsy of the right submandibular lesion (HepPar-1 positive, Arginase-1 positive, Ki-67 about 40 percent) confirmed hepatic origin. Multiple bone metastases were identified in June 2024. The manubrial lesion enlarged from 48 x 68 mm to 77 x 92 mm to 89 x 107 mm, with TGR values of about 16.6 percent per month and 4.3 percent per month. After about 18 months of radiologic stability, progression was documented in May 2025. Over 22 months, liver function remained relatively stable; ascites first appeared in July 2025. No grade 3 or higher adverse events were documented.

Conclusion: TGR may complement RECIST 1.1 by detecting growth-kinetic shifts during transition from stable disease to progression. Integrated traditional Chinese medicine plus regorafenib may help preserve hepatic reserve and treatment continuity.

LBP2-6 10271

Triple Trouble: A Case of Hepatocellular Carcinoma in a Patient with Previous Renal and Colonic Malignancies

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Background: Multiple primary tumors (MPTs) are two or more synchronous or metachronous primary malignancies in a single patient. The frequency ranges from 2% to 17%, with triple primary cancers being exceedingly rare. We report a case of a patient with three primary malignant tumors: Renal cell carcinoma, colon adenocarcinoma and hepatocellular carcinoma.

Methods: We describe the clinical course, imaging findings, histopathology, and management of a 74-year-old male with a history of synchronous renal cell carcinoma and stage IA colon adenocarcinoma diagnosed in 2008, both managed surgically with partial nephrectomy and left hemicolectomy. In 2025, the patient developed progressive weight loss with elevated AST, ALT, carcinoembryonic antigen, and PIVKA-II (441.42 mAU/mL). Magnetic resonance imaging of the whole abdomen was performed, followed by ultrasound-guided liver biopsy for definitive diagnosis.

Results: Imaging revealed a large right hepatic mass demonstrating arterial phase hyperenhancement and washout, initially suggestive of metastatic disease. Histopathologic examination showed hepatocytes arranged in trabecular patterns with positive Arginase and Glypican-3 immunostaining, confirming a diagnosis of hepatocellular carcinoma rather than metastatic recurrence. Based on this diagnosis, the patient was planned for combination therapy with selective internal radiation therapy (SIRT) and immunotherapy.

Conclusion: This case underscores the importance of considering de novo hepatocellular carcinoma in patients with prior malignancies presenting with hepatic lesions. Biopsy confirmation remains crucial when imaging findings are inconclusive. Recognition of multiple primary cancers allows appropriate treatment selection, including liver-directed therapy, and emphasizes the need for vigilant long-term surveillance to improve patient outcomes.

A CT-Based Hybrid Model for Predicting CK19-Positive Hepatocellular Carcinoma and Assessing Prognosis: A Multicenter Study

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Background: Cytokeratin 19 (CK19)-positive hepatocellular carcinoma (HCC) is an aggressive subtype associated with early recurrence, metastasis, and poor prognosis.

Methods: This retrospective multicenter study included 509 patients with HCC from five hospitals (2012-2023). Patients were divided into training, internal test (n=382) and external test (n=127) sets. A hybrid model integrating clinical variables, CT semantic features, and radiomics signatures was developed. Feature selection was performed using maximum relevance minimum redundancy (mRMR) and least absolute shrinkage and selection operator (LASSO) regression. Model performance was evaluated using area under the receiver operating characteristic curve (AUC). Prognostic stratification and treatment subgroup analyses were conducted using Kaplan - Meier survival analysis and propensity score matching (PSM).

Results: The hybrid model demonstrated AUCs of 0.80 (95% CI: 0.70-0.89) and 0.76 (95% CI: 0.66-0.87) in the internal and external test sets, respectively, outperforming clinical-only (AUCs: 0.689-0.652) and radiomics-only (AUCs: 0.712-0.722) models. The model successfully stratified patients into high- and low-risk groups, with the high-risk group showing significantly worse overall survival (OS) and early recurrence-free survival (eRFS). Subgroup analyses suggested that high-risk patients may benefit from minimally invasive surgery and wider resection margins, but not from postoperative adjuvant transarterial chemoembolization.

Conclusion: A CT-based hybrid model can noninvasively predict CK19-positive HCC and stratify prognosis, offering potential for personalized surgical planning and risk-adapted management.

LBP3-2 10263

Development of a Novel Erythrocyte-Related Risk Score for Prognosis Prediction in Hepatocellular Carcinoma Patients

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Background: Hepatocellular carcinoma (HCC), a highly dangerous malignancy to human health, requires accurate prognostic tools. In this study, we developed a novel risk score related to erythrocyte to predict the prognosis of HCC patients.

Methods: HCC datasets were obtained from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases, while a gene set related to erythrocyte development and differentiation was obtained from Molecular Signature Databases. Using the least absolute shrinkage and selection operator (LASSO) regression model, we developed the risk score on erythrocyte-related genes. Additionally, a user-friendly visualization model was established, incorporating clinical parameters, to evaluate its calibration, accuracy, and clinical utility. The relationship between the erythrocyte-related risk score and molecular pathways, immune cells, and functions was explored, along with the predictive abilities of the hub genes across various cancer prognoses.

Results: The study found that the erythrocyte-related risk score effectively differentiated the prognosis of HCC patients and was associated with molecular and immune-related features, providing new strategies for personalized treatment.

Conclusion: This investigation has developed a risk scoring system based on genes associated with erythrocyte development, which can predict OS and PFS in patients with HCC. Additionally, this risk scoring system can provide insight into immune cell infiltration and their response to anti-tumor treatment in patients.

Anemia Predicts Poor Prognosis in HBV-Related Hepatocellular Carcinoma: a Large-Scale Retrospective Study

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Hepatitis B virus-related hepatocellular carcinoma (HBV-HCC) poses a major global health burden. While anemia correlates with tumor progression and prognosis in various cancers, its specific role in HBV-HCC is unclear. This study examined anemia as an independent prognostic factor for long-term survival, identifying potential therapeutic targets. **Methods:** This retrospective cohort included 2,642 newly diagnosed HBV-HCC patients at Beijing Ditan Hospital (January 2008 to December 2019), divided into anemia (n=911) and non-anemia (n=1,731) groups. Baseline characteristics were compared. Scatter plots assessed hemoglobin correlations with clinical parameters. Multivariate Cox regression identified prognostic factors. Kaplan-Meier curves evaluated 5-year overall survival (OS) and progression-free survival (PFS) by anemia severity and subgroups (BCLC stages, Child-Pugh classes, portal vein tumor thrombosis [PVTT] status). **Results:** Anemia group had higher hyperlipidemia, cirrhosis, complications, tumor burden, HBV-DNA positivity, and conservative treatment rates, with lower antiviral therapy. Anemia was an independent risk factor for 5-year OS. Anemic patients showed lower 5-year OS (median survival: 28.4 vs. 45.2 months) and PFS, worsening with severity. In BCLC A-B, Child-Pugh A-B, and no-PVTT subgroups, anemic patients had significantly inferior OS. **Conclusions:** Anemia independently worsens 5-year OS in HBV-HCC, linking to liver dysfunction, tumor burden, and complications. It represents a novel therapeutic target, especially in early-stage (BCLC A-B), preserved-function (Child-Pugh A-B), and no-PVTT patients.

Assessment of Liver Fibrosis Severity in Patients Infected with Hepatitis B and C Viruses

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Background: According to the World Health Organization (WHO), cancer-related deaths are projected to reach 20.3 million by 2030 due to global population growth. Hepatocellular carcinoma is a leading cause of cancer deaths and is strongly associated with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Mongolia has the highest liver cancer mortality rate worldwide. This study assessed liver fibrosis severity in HBV- and HCV-infected patients and its association with age and sex.

Methods: A cross-sectional study was conducted using medical records of 90 patients treated at Happy Veritas Hospital. Biochemical parameters, including ALT, AST, and platelet count (PLT), were collected. Liver fibrosis severity was assessed using the FIB-4 index, and APRI scores were calculated.

Results: Elevated ALT, AST, and bilirubin indicated hepatic inflammation. Most patients had mild to moderate fibrosis. Age-stratified analysis showed higher advanced fibrosis in older groups: 40% in patients aged 30-39, 52% in 40-49, and 42.9% in 50-59. Among males, mild, moderate, and advanced fibrosis were 42.9%, 21.4%, and 35.7%, while in females, mild and advanced fibrosis were 39.6%. Advanced fibrosis was slightly more frequent in HCV-infected patients than HBV-infected patients (40% vs 36.2%), not statistically significant.

Conclusion: Liver fibrosis severity increases with age in chronic HBV and HCV patients. APRI and FIB-4 indices are useful non-invasive tools to identify patients at higher risk of advanced fibrosis.

Level of IL-6 is Directly Correlated with the Severity of Hepatitis B

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Introduction: Hepatitis B virus (HBV) causes hepatitis, fulminant hepatic failure, liver cirrhosis and hepatocellular carcinoma. Cytokines have been shown to be engaged in regulating hepatocyte functions, and play an important role in HBV infection immunopathogenesis.

Method: About 52 HBV subjects ranging from 18 years old to 80 years old that were recruited. Venous blood was taken and centrifuged at 4500rpm. The sera were withdrawn and divided into two aliquots and kept under temperature of -20 to -70 degrees. The first group of sera were subjected to a hybrid capture, tube-based signal amplification using HBV Digene Hybrid-Capture I, Digene Corporation, USA. While the second group of sera were subjected to a sandwich-ELISA test using LEGEND MAX Deluxe set human IL-6 kit to quantify the IL-6 levels. Both data were recorded and analyzed using IBM SPSS version 26 software.

Results: The severe the infection, the higher the IL-6 level, taking the mean value of IL-6 as 132.6pg/ml. A linear scatter plot was derived between the levels of IL-6 and HBV viral load. Pearson correlation coefficient showed a linear correlation between the two variables. Higher levels of IL-6 were detected in the subjects with HBV for longer than 6 months which proved that IL-6 levels correspond to the chronicity of the disease.

Conclusion: IL-6 is an acute phase reactant in the liver. Our studies proved that serum IL-6 levels were positively correlated with HBV severity and chronicity. Thus, IL-6 may be a useful indicator of disease activity and therapeutic efficacy in hepatitis B patients.

The Mongolian and the Southeast Asian Cluster: Mapping the 2022 Liver Cancer Epidemic Across Asia

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Background: Liver and intrahepatic bile duct carcinoma represents a critical oncological burden in Asia. This study elucidates the sexual dimorphism and regional heterogeneity of its incidence in 2022.

Methods: We analyzed incidence data extracted from the 2022 global cancer observatory (GLOBOCAN) database, covering 47 Asian countries/territories. Indices included Age-Standardized Rates (ASR) per 100,000 and absolute case volumes, stratified by sex.

Results: The analysis reveals profound geographic variance and consistent male predominance. Mongolia exhibits hyper-endemic status, recording the highest ASRs globally (Male: 113.46; Female: 80.95). A significant high-incidence cluster was identified in Southeast Asia (Cambodia, Thailand, Vietnam), where male ASRs exceed 34.0. China bears the highest absolute disease burden (> 367,000 combined cases), driven by population size rather than extreme ASRs relative to Mongolia. Conversely, South and West Asian nations (e.g., India, Israel) show the lowest incidence (ASR < 5.0). Sexual disparity is pronounced, with male-to-female ratios exceeding 3:1 in high-incidence zones.

Conclusion: The 2022 data highlights a persistent public health crisis in East and Southeast Asia. The extreme incidence in Mongolia and the massive volume in China necessitate stratified health policies prioritizing viral hepatitis eradication and targeted surveillance in high-risk male populations.

LBP4-2 10264

Temporal Trends in Hepatocellular Carcinoma Mortality in a Historically High-Risk Region of Japan: A Population-Based Study from Yamanashi Prefecture

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Background: Yamanashi Prefecture has historically exhibited one of the highest prevalences of hepatitis C virus (HCV) infection in eastern Japan. This unique epidemiological background is largely attributable to iatrogenic transmission during intravenous treatment for schistosomiasis japonica, which was once endemic in the region. Consequently, Yamanashi had long been regarded as a region with an exceptionally high incidence of hepatocellular carcinoma (HCC).

Objective: This study aimed to evaluate temporal trends in age-standardized mortality from HCC in Yamanashi Prefecture and to compare these trends with national data in Japan.

Methods: Publicly available epidemiological statistics were analyzed to assess age-standardized HCC mortality rates in Yamanashi Prefecture and nationwide. Longitudinal data over multiple decades were examined, with particular emphasis on recent trends.

Results: Age-standardized HCC mortality in Yamanashi Prefecture was substantially higher than the national average in earlier periods. However, a marked and sustained decline was observed over time. In recent years, the mortality rate in Yamanashi has decreased to a level comparable with the national average, indicating a significant narrowing of the regional disparity.

Discussion: The substantial reduction in HCC mortality in a historically high-risk region suggests major improvements in HCC management. Widespread HCV eradication, establishment of systematic surveillance, and advances in therapeutic strategies may have collectively contributed to improved survival outcomes at the population level.

Long-term Trends in Incidence, Stage, and Survival of Hepatitis B Virus-Related Hepatocellular Carcinoma: A Prospective Cancer Registry Analysis from 2006 to 2024

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Background: Hepatitis B virus-related hepatocellular carcinoma (HBV-HCC) remains a major cause of liver cancer in the Asia-Pacific region. However, long-term temporal changes in incidence, disease stage at diagnosis, and survival in the real-world setting have not been fully elucidated. Leveraging a long-standing prospective cancer registry, we evaluated longitudinal trends in HBV-HCC and compared them with hepatitis C virus-related (HCV-HCC) and non-B non-C HCC (NBNC-HCC).

Methods: Using a prospective institutional cancer registry covering 25 malignancies, we analyzed 33,140 cancer cases registered between October 2006 and December 2024. Among 1,086 hepatocellular carcinoma cases, 69 HBV-HCC cases were identified. Patients were divided into three periods: early (2006-2011), middle (2012-2017), and late (2018-2024). Incidence, UICC stage distribution, and overall survival were compared across periods and etiologies. Fisher's exact test, chi-square test, and log-rank test were applied.

Results: The number of HBV-HCC cases significantly declined in the late period, similar to HCV-HCC, while NBNC-HCC significantly increased. Unlike HCV-HCC, which showed a significant shift toward earlier-stage diagnosis, HBV-HCC demonstrated no significant stage migration across periods ($p=0.356$). Overall survival of HBV-HCC did not significantly improve over time, whereas survival significantly improved in both HCV-HCC and NBNC-HCC in the late period.

Conclusion: Although the incidence of HBV-HCC has markedly decreased, no significant improvement in stage at diagnosis or survival was observed. Further studies are needed to clarify the impact of functional cure of HBV on hepatocarcinogenesis and long-term outcomes.

Increasing Proportion but Stable Incidence of Non-B Non-C Hepatocellular Carcinoma in the Post-DAA Era: A Real-World Cohort Study

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Background: With the widespread use of direct-acting antivirals (DAAs), the etiology of hepatocellular carcinoma (HCC) has been shifting from virus-related to non-viral causes. However, nationwide fieldwork across Japan is not practically feasible. Therefore, analyses based on large real-world data from key regional medical centers, particularly those covering a substantial proportion of the prefectural population, are essential. Whether the increasing proportion of non-B non-C (NBNC) HCC reflects a true increase in patient numbers remains unclear.

Aim: To clarify temporal changes in both the proportion and absolute number of NBNC-HCC patients using a large real-world cohort.

Methods: We analyzed 1,120 HCC patients diagnosed at a single center between 2006 and 2024. Etiology was classified as hepatitis B virus (HBV), hepatitis C virus (HCV), or NBNC. Annual proportions and absolute numbers were assessed, with particular focus on changes before and after the introduction of DAA therapy in 2015.

Results: The proportion of HBV-related HCC remained stable throughout the study period. In contrast, the proportion of HCV-related HCC declined markedly after 2015 following widespread DAA use. Consequently, the proportion of NBNC-HCC increased over time, whereas the absolute number of NBNC-HCC patients remained largely unchanged.

Conclusion: The increasing proportion of NBNC-HCC primarily reflects a decline in HCV-related HCC after effective antiviral therapy rather than a true increase in NBNC-HCC incidence, highlighting a paradigm shift in HCC etiology in the post-DAA era.

Efforts to Combat Hepatitis C in a Leading High-Prevalence Prefecture in Eastern Japan

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Background: The prevalence of hepatitis C virus (HCV) infection has declined following the introduction of direct-acting antiviral (DAA) therapy. Because asymptomatic hepatocellular carcinoma (HCC) is difficult to detect, early identification and treatment of viral hepatitis are essential for HCC prevention. Yamanashi Prefecture is a high-prevalence region in eastern Japan, partly due to historical parenteral administration of antischistosomal therapy for schistosomiasis japonica, a former endemic disease in this area. Although nationwide fieldwork is challenging, our institution provides medical care for approximately 30% of the prefectural population, enabling assessment of HCV status at the prefectural level and providing a basis for future nationwide fieldwork.

Methods: Between January 2008 and December 2025, 184,428 individuals who underwent anti-HCV antibody testing at our institution were included. Annual anti-HCV antibody positivity rates, HCV-RNA testing rates, and HCV-RNA positivity rates were analyzed.

Results: In 2008, the anti-HCV antibody positivity rate was 7.4%, the HCV-RNA testing rate was 18.6%, and the HCV-RNA positivity rate was 55.6%. By 2025, these values changed to 1.6%, 57.9%, and 8.8%, respectively. Over time, anti-HCV antibody positivity and HCV-RNA positivity decreased, whereas HCV-RNA testing increased.

Conclusions: The decline in HCV-RNA positivity suggests that DAA therapy introduced in 2015 has substantially advanced HCV elimination. However, complete elimination has not yet been achieved. Improving HCV-RNA testing rates and awareness among physicians in other specialties remains essential.

Advancing Toward WHO's HCV Zero Goals: Performance Evaluation of the Elecsys HCV Duo for Simultaneous Antibody and Core Antigen Detection

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Background: Hepatitis C virus (HCV) diagnosis typically requires sequential HCV antibody (HCV-Ab) and HCV-RNA testing, which can delay confirmation. The Elecsys HCV Duo (HCV Duo) enables simultaneous detection of HCV-Ab and HCV core antigen (HCV-Ag) from a single serum sample. This study evaluated the performance of HCV Duo and the utility of HCV-Ag.

Methods: A total of 1,335 serum samples were analyzed to assess concordance of HCV-Ab results between HCV Duo and the Alinity Anti-HCV assay. HCV-Ag detection was examined in 18 HCV-RNA positive samples. Longitudinal changes in HCV-Ag and HCV-RNA were compared in five patients receiving antiviral therapy over two months.

Results: HCV-Ab concordance between HCV Duo and Alinity Anti-HCV was 100% (1,355/1,355). Among 1,335 samples, 1,298 were Ab-/Ag-, 2 were Ab-/Ag+, 32 were Ab+/Ag-, and 3 were Ab+/Ag+. Of the 18 HCV-RNA positive samples, 13 (72%) were Ag positive. In treated patients, HCV-Ag generally became negative one month after therapy initiation, paralleling HCV-RNA kinetics, with minor early discrepancies.

Conclusion: The HCV Duo assay reliably detects HCV-Ab and shows good concordance between HCV-Ag and active infection. Simultaneous Ab/Ag detection may streamline diagnostic workflows, support earlier identification of active infection, and reduce reliance on HCV-RNA testing.

Identification of Patients with Positive Hepatitis Virus Markers by Hepatitis Medical Care Coordinators

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Background: In May 2016, the World Health Organization announced a global strategy to eliminate hepatitis C virus (HCV) infection by 2030, emphasizing the importance of systematic identification of infected individuals.

Aim: To evaluate the effectiveness of a multidisciplinary program led by Hepatitis Medical Care Coordinators in identifying patients with positive hepatitis virus markers in a general hospital.

Methods: Since 2019, an in-hospital identification program centered on Hepatitis Medical Care Coordinators has been implemented. For anti-HCV-positive cases, 18,043 inpatients and outpatients who underwent anti-HCV antibody testing between July 2018 and March 2025 were included. Laboratory coordinators extracted positive cases, pharmacy coordinators prepared clinical summaries, and gastroenterologists reviewed cases before recommending referral. For hepatitis B surface antigen positive cases, 17,558 patients tested between January 2019 and March 2025 were evaluated using the same workflow.

Results: Anti-HCV antibodies were detected in 903 patients (5.0%), of whom 395 newly identified cases required referral recommendations. Among these, 157 patients (40%) were already managed by the Department of Gastroenterology at the initial visit, and 92 patients (23%) visited the department following coordinator-led recommendations. Among these patients, 42 (46%) were negative for HCV RNA, and 9 received direct-acting antiviral therapy. Among 16 patients with liver cirrhosis, hepatocellular carcinoma (HCC) was diagnosed in 5 patients, and hepatic resection or local ablative therapy was performed in 4. The hepatitis B surface antigen positivity rate was 476(2.7%), and 232 newly identified patients required referral recommendations.

Conclusion: A coordinator-led multidisciplinary approach promoted identification, specialist referral, and early detection of HCC, supporting hepatitis elimination strategies.

Single-Cell Profiling Reveals Novel Insights into Vessel Co-Option in Human Colorectal Liver Metastases

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Colorectal cancer liver metastases (CRCLM) develop through two major histopathological growth patterns: desmoplastic (dHGP), which depends on angiogenic vessel formation, and replacement (rHGP), which expands by co-opting the native liver vasculature. The molecular mechanisms underlying vessel co-option remain incompletely understood. We performed single-nucleus RNA sequencing on snap-frozen CRCLM tissues from both patterns across 10 donors. After data integration and clustering, we annotated liver, stromal, immune, and vascular compartments, focusing on endothelial and cancer cell heterogeneity. Differential gene expression and CellChat-based ligand-receptor analyses identified signaling pathways enriched in vessel-co-opting regions. Key findings related to endothelial cell activation were tested in primary liver sinusoidal endothelial cells exposed to conditioned medium or extracellular vesicles from patient-derived organoids. Endothelial cells exhibited distinct transcriptional states. Replacement lesions showed increased expression of adhesion-, integrin-, and cytoskeleton-related genes consistent with remodeling and mechanical adaptation, whereas desmoplastic lesions displayed signatures of endothelial proliferation and sprouting angiogenesis. Tumor-derived conditioned media partially reproduced these states in vitro. Our data define growth pattern-specific endothelial programs linked to vessel co-option and angiogenesis in CRCLM, highlighting vascular heterogeneity and candidate pathways that may affect therapeutic response.

Unbiased Single-Cell Transcriptome-Proteome Co-Profiling Reveals Post-Transcriptional Buffering in Rare CSF-CTCs

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Simultaneous profiling of the transcriptome and proteome is essential for decoding regulatory mechanisms but remains constrained by sensitivity trade-offs and the bias inherent in targeted approaches. Here, we present a single-cell Magnetic-Assisted Partitioning Sequencing (scMAPS) strategy for unbiased simultaneous transcriptome-proteome profiling within the same single cell. By chemically segregating RNA and proteins without physical splitting, scMAPS minimizes sample loss and obviates special device. We demonstrate its precision in multi-modal cell-type classification and marker cross-validation. Furthermore, by combining scMAPS and microfluidic chips to rare cerebrospinal fluid circulating tumor cells (CSF-CTCs) from lung cancer patients, we uncover a coordinated malignant dormancy phenotype characterized by synchronized immune evasion and metabolic suppression. Validated against clinical cohort data, these findings highlight the power of scMAPS to dissect complex post-transcriptional buffering mechanisms. This robust workflow democratizes single-cell proteogenomics, offering a versatile platform for deep phenotyping across diverse biological systems, from complex tissues to scarce clinical specimens.

Research on Targeted TGF-beta Pathway Inhibitors in Hepatocellular Carcinoma

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Objective: TGF-beta signaling promotes HCC progression and therapy resistance. This study reviews preclinical/clinical advances of its inhibitors in HCC, summarizing mechanisms, efficacy, safety, combinations and key challenges.

Methods: PubMed/Embase/ClinicalTrials.gov were searched for relevant studies updated to February 9, 2026; agents were grouped by modality.

Results: ALK5 inhibition suppresses SMAD/EMT/angiogenesis, reducing HCC invasion. TGF-beta blockade relieves immune exclusion and enhances PD-1/PD-L1 therapy. It also intercepts the fibrosis-cirrhosis-cancer axis, supporting stage-adapted combinations.

Conclusion: Targeting TGF-beta reshapes HCC's TME and limits metastasis. Future research should refine predictive biomarkers, optimize combination timing and clarify long-term safety.

Research on Targeted FGFR4 Inhibitors in Hepatocellular Carcinoma

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Background: The fibroblast growth factor 19 (FGF19)-FGFR4-KLB axis is liver-enriched and links bile-acid homeostasis to oncogenic signaling. In hepatocellular carcinoma (HCC), pathway activation promotes proliferation, survival, and therapeutic resistance, nominating FGFR4 as a precision target. We review recent advances in FGFR4-targeted inhibitors and biomarker-driven combination strategies in HCC.

Methods: PubMed, Embase, and ClinicalTrials.gov were searched for preclinical and clinical studies of FGFR4 inhibition in HCC (updated February 9, 2026). Agents were grouped as selective FGFR4 inhibitors or pan-FGFR inhibitors with FGFR4 activity, and evidence was synthesized around efficacy, biomarkers, safety, resistance, and combinations.

Results: (1) Biomarker-enriched anti-tumor activity: Clinical benefit is mainly observed in FGF19-driven tumors. In a first-in-human study of fisogatinib (BLU-554), objective response rate (ORR) was 17% in FGF19 immunohistochemistry (IHC)-positive patients, with no objective responses in FGF19-negative/unknown tumors. (2) On-target pharmacology and safety: Because FGFR4 regulates bile-acid feedback, class toxicities include diarrhea and bile-acid perturbation; in fisogatinib once-daily cohorts, diarrhea occurred in 74% of patients and was grade greater than or equal to 3 in 8%, supporting proactive supportive care and monitoring. (3) Resistance and combination strategies: Acquired on-target FGFR4 kinase-domain mutations and bypass signaling can limit durability, motivating next-generation inhibitors and biomarker-enriched combinations.

Conclusion: FGFR4 inhibition represents a biomarker-driven therapeutic avenue for FGF19-activated HCC. Future studies should harmonize FGF19/FGFR4/KLB assays, integrate dynamic resistance monitoring, optimize combination timing, and refine bile-acid-related toxicity mitigation to improve depth and durability of response.

Development of a Novel Flavonoid Derivative with a Potent Anti-steatosis Activity in HepG2 Cells for Therapeutic Use in Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)

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Metabolic dysfunction associated steatotic liver disease (MASLD), a chronic liver disease previously known as non-alcoholic fatty liver disease (NAFLD), is a global health concern with a prevalence of about 30% worldwide. Uncontrolled MASLD leads to liver fibrosis that ultimately resulting in cirrhosis, liver failure, or hepatocellular carcinoma, causing significant burden to the patients and the healthcare system. Treatment of MASLD mainly employs lifestyle modifications such as diet controls. However, lack of patient compliance to lifestyle modifications is the key factor affecting the low rate of successful MASLD management. Resmetirom, a thyroid hormone receptor beta agonist, is a single drug that has been approved by the United States Food and Drugs Administration (USFDA) in 2024 for use in MASLD patients. However, alternative drugs/regimens are still in need as resmetirom safety profiles in clinical use are limited and further studies are still required to evaluate the true drug adverse effects. With natural compound libraries in our hands and HepG2 human hepatoma cell-based fluorescence high-throughput steatosis model, we found that a flavonoid derivative AD14, without any cytotoxic activity observed at any concentrations tested, exhibited anti-steatosis activity in HepG2 cells in a dose-dependent manner with half-maximal inhibitory concentration (IC₅₀) at 186 nanomolar. In addition, flow cytometric analysis at the single cell level showed that AD14 had higher anti-steatosis activity than resmetirom. This study suggests that our AD14 could be a promising therapeutic agent for use in MASLD, however further animal and clinical studies are needed to assess its toxicity/adverse effects.

LBP6-2 10247

A Systematic Evaluation of Network Pharmacology Approaches for Elucidating Mechanisms and Therapeutic Effects of Herbal Medicines

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Background: Network pharmacology has become an increasingly popular approach for uncovering the mechanisms and therapeutic benefits of herbal remedies. However, the wide variability in current methodologies highlights a critical need for systematic assessment to guarantee consistency and reliability. Therefore, this study aimed to critically evaluate network pharmacological strategies, focusing on their ability to identify the underlying mechanisms and therapeutic efficacy of herbal medicines.

Methods: We utilized a holistic strategy encompassing systematic data collection, network construction, and analytical evaluation. Constituents and targets of herbal medicines were rigorously sourced from five separate databases to ensure robust coverage and high data integrity. We applied advanced network algorithms to isolate key targets and forecast therapeutic outcomes, thereby enhancing the analysis's scope. Furthermore, computational predictions were substantiated through experimental validation using prostate cancer models.

Results: Performance evaluations revealed unique trends depending on the network construction and aggregation techniques employed. While methods such as network centrality and path counts demonstrated specific advantages and limitations, assessing the influence on the multiscale interactome provided the superior accuracy in distinguishing known therapeutic effects. By optimizing these conditions, we successfully discovered novel indications for herbal treatments, which were subsequently confirmed via in vitro and in vivo assays.

Conclusion: This research offers a pioneering, comprehensive critique of existing network pharmacology methodologies within the field of herbal medicine. The findings provide essential guidelines for enhancing the precision and reliability of future studies aimed at elucidating the mechanisms and therapeutic potential of herbal drugs.

The Mechanism of Compound Kushen Injection in Regulating Phosphatidylcholine-Mediated NK Cell Suppression of Liver Cancer Ascites

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Background: This study aims to explore the mechanism of action of Compound Kushen Injection in the treatment of malignant liver cancer ascites and identify the related drugs and their target points involved in inhibiting ascites formation.

Methods: The study utilized the Balb/c mouse liver cancer ascites model, divided into four groups: control, low-dose Compound Kushen Injection, medium-dose, and high-dose. Mice were treated for 15 days with different doses of the injection. The changes in metabolic and immune environments of the ascites were assessed using LC-MS, H&E staining, immunohistochemistry, and flow cytometry to analyze immune cell variations.

Results: Compared with the control group, the medium and high doses of Compound Kushen Injection significantly inhibited ascites formation, with reductions of 11.6% and 19.9% in ascites volume, respectively. The median survival time increased by 22.5% and 37.8%. Metabolomic analysis showed alterations in phosphatidylcholine and other metabolites, especially in the COP-choline metabolic pathway. Histological and immunological analysis revealed significant reductions in peritoneal hyperplasia, fibrosis, and immune cell infiltration.

Conclusion: Compound Kushen Injection significantly reduces ascites in the malignant liver cancer mouse model, primarily by regulating phosphatidylcholine metabolism and enhancing immune responses. This study provides experimental evidence for its potential application in liver cancer ascites treatment and lays the foundation for future clinical use.

LBP6-4 10261

Efficacy of Yangyin Fuzheng Jiedu Prescription for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: An Evaluation Using Five Propensity Score Methods

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Objectives: adjuvant therapy selection for advanced hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) remains challenging. This study evaluated Traditional Chinese Medicine (TCM)'s value in improving outcomes, comparing hospital-prepared Yangyin Fuzheng Jiedu Formula (YFJP) decoction with approved Chinese patent medicines (CPMs) like Ganfule Capsule and Huaier Granule.

Methods: We retrospectively analyzed 892 HCC patients with PVTT treated 2012 to 2022, divided into Western medicine (WM; n=579) and integrated Chinese-Western medicine (ICWM; n=313) groups. WM followed 2019 guidelines (antitumor, antiviral, anti-inflammatory, complication, and supportive care). ICWM added YFJP. TCM duration was from records. Propensity score matching and weighting adjusted confounders. Multivariable Cox models identified 5-year overall survival (OS) factors. Forest plots assessed HR differences across subgroups; Kaplan-Meier curves compared TCM patterns/durations/types; STEPP analysis identified YFJP-benefiting subpopulations.

Results: After adjustment using propensity score methods, TCM therapy was identified as an independent protective factor for prognosis in PVTT patients. Other independent factors influencing 5-year OS included etiology, WM treatment modality, platelet count, creatinine level, gamma-glutamyl transferase level, alpha-fetoprotein level, mean platelet volume, and CD8+ T-cell count. Prolonged duration of TCM administration was associated with a stronger protective effect on prognosis, indicating greater patient benefit. STEPP analysis revealed that patients with mild to moderate thrombocytopenia, prothrombin activity approaching 70%, or an inflammatory burden index greater than 4 derived significantly more benefit from the YFJP decoction than from CPMs.

Conclusion: Long-term TCM adjunct improves PVTT prognosis; CPM efficacy confirmed. YFJP benefits subgroups with better coagulation or severe inflammation, warranting mechanistic studies.

Yangyin Fuzheng Jiedu Prescription Improves Survival in HBV Related Hepatocellular Carcinoma Patients with Anemia: A Promising Herbal Formula Under Translation

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Objective: This study aimed to identify independent prognostic factors for patients with concurrent hepatitis B virus-related hepatocellular carcinoma (HCC) and cancer-related anemia (CRA), and to investigate the impact of compound Yangyin Fuzheng Jiedu Prescription (YFJP) on patient outcomes. Furthermore, the objective was to determine the patient subset most likely to benefit from YFJP intervention for guiding clinical practice.

Methods: A total of 532 patients diagnosed with coexisting HBV-related HCC and CRA at Beijing Ditan Hospital between June 2008 and June 2017 were analyzed, with 318 receiving YFJP treatment and 214 undergoing exclusive modern medical treatment. Multivariable Cox regression analysis was employed to assess the effect of YFJP on hazard ratio (HR), while Kaplan-Meier survival curves and dendrograms were used to examine mortality risks and factor correlations among HBV-HCC patients with CRA.

Results: The Cox regression analysis revealed that YFJP was a significant protective factor for 1-year survival in this patient cohort. Patients using YFJP for over 6 months showed significantly higher overall survival rates compared to those using it for less than 6 months. Alpha-fetoprotein (AFP) and C-reactive protein (CRP) emerged as independent risk factors for 1-year survival in HBV-HCC patients with CRA, with the highest survival rates observed in subgroups having low AFP and CRP levels.

Conclusion: YFJP demonstrated protective effects in patients with HBV-related HCC and CRA, and survival was positively associated with the duration of YFJP use. Patients with low CRP and AFP levels represent the optimal population for YFJP treatment to enhance prognosis.