Table 1: Multivariable regression of factors associated with HCC

	Adjusted odds ratio	95% confidence interval
Age, in years	1.034	1.032 – 1.036
Sex		
Male is reference		
Female	2.566	2.472 - 2.663
Hepatitis C	5.861	5.320 – 6.457
Hepatitis B		
HBV monoinfection is reference		
HBV/HDV coinfection	1.558	1.222 – 4.042
Metabolic associated steatohepatitis	3.030	2.807 – 3.270
Race		
White is reference		
Black	1.526	1.458 – 1.597
Hispanic	1.628	1.557 – 1.703
Asian	4.287	4.011 – 4.583
Native American	1.441	1.226 – 1.693
Insurance		
Medicare is reference		
Medicaid	1.090	1.038 – 1.144
Private	1.509	1.442 – 1.580
Self-pay	0.869	0.789 – 0.958

Mo1472

DIFFERENTIATION OF BILIARY STRICTURE WITH LIQUID BIOPSY USING BILE AND ITS DEVELOPMENT INTO TREATMENT

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Objective: Biliary stricture is found not only in malignant but also in benign diseases, and it is sometimes difficult to differentiate between them. Endoscopic retrograde cholangiopancreatography is used to confirm the diagnosis, but biopsy with fluoroscopic imaging is inaccurate and the sensitivity is only approximately 30% because of the small size of the specimen obtained. Recently, the usefulness of liquid biopsy using blood has been reported, but it has not been applied to bile, which is expected to contain more tumor cells. In this study, we performed liquid biopsy using bile collected from patients with biliary stricture and examined the possibility of differential diagnosis between benign and malignant diseases and their application to treatment. Methods: Eighty bile samples collected from 80 patients with biliary stricture were subjected to cytological diagnosis and genomic analysis. OncoKB was used to identify oncogenic and actionable mutations and to detect therapeutic targets. Malignancy was determined by cytological diagnosis as Class IV or V, and by genomic analysis as identification of oncogenic mutations, and the diagnostic performance of both was evaluated. Results: The diagnosis of malignancy was made in 21% (10/47) by cytological diagnosis, while 66% (31/47) by genomic analysis ($P < 0.001$). On the other hand, oncogenic mutations were detected in 13 benign patients, of which 4 (31%) were subsequently diagnosed as malignant during the follow-up period. Among them, the median time from bile collection to malignant diagnosis was 390 days. Of the 47 patients with malignancy, mutations with FDA-approved drugs were detected in 16 (34%). Conclusion: Liquid biopsy using bile may be useful in the differentiation of benign and malignant diseases and in the search for therapeutic agents and may also be applicable to early diagnosis.

Mo1473

PREVALENCE OF RARE GERMLINE VARIANTS IN HEPATOCELLULAR CARCINOMA IN A GLOBAL MULTI-ETHNIC CASE-CONTROL GENETIC ASSOCIATION STUDY

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Background & Aims: Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer-related deaths globally, mainly driven by well-established environmental and lifestyle risk factors, with an important but poorly understood inherited genetic component. The prevalence of pathogenic/likely pathogenic germline variant (PGVs) in cancer-associated genes has varied across studies and has not been examined in African or Latin American populations. Thus, we aimed to complete a multi-ethnic study to determine whether rare PGVs can be identified among individuals with HCC and explore differences among geographic settings and ethnic backgrounds in three continents.
Methods: We enrolled 452 patients diagnosed with HCC through pathology and/or radiology reports across various global sites, including the United States, Africa (Ghana and Nigeria), and South America (Argentina, Brazil, Chile, Colombia, Ecuador, and Peru). We also curated controls comprising 2,813 cancer-free patients from the same sites (excluding South America). Whole exome sequencing (WES) was performed on all subjects. The analysis focused on 6 cancer-associated genes (*BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *MSH6*, and *PMS2*), previously identified in multiple HCC studies. Extracted variants were annotated using the variant effect predictor (VEP), with subsequent filtering focused on rare variants (maximum minor allele frequency <0.01 or absent). Variants not classified as PGVs on ClinVar underwent classification and filtering based on InterVar analysis. The rates of PGVs of the 6 cancer-associated genes were compared using Fisher's exact test with p value reported.
Results: Within our global HCC population of 452 patients, we discovered PGVs in 16 individuals (3.54%). The HCC population was as follows: Africa (3 out of 122, 2.46%), South America (4 out of 89, 4.49%), and the United States (9 out of 241, 3.73%). The prevalence of PGVs in the control population (n=2,813) was 1.71%; breakdown was as followed: Africa (6 out of 404, 1.49%) and United States (42 out of 2,409, 1.74%). We found a statistically significant difference in total gene burden of PGVs between the HCC cases and cancer-free controls (p=0.016). In South American and African samples, there was higher prevalence of *FANCA* variants, while in the United States samples *BRCA2* variants were seen more frequently, but these differences did not reach statistical significance (**Figure 1**).
Conclusions: This is the first multi-ethnic global study of hereditary genetics in HCC. There was a significant enrichment in PGVs in 6 genes in patients with HCC across various ethnicities. These findings could impact clinical guidelines for screening and personalized treatment of patients with HCC.

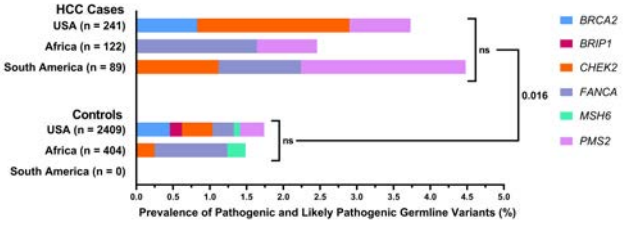

Figure 1: Graph showing the prevalence of pathogenic and likely pathogenic alleles in HCC cases and controls.

Mo1474

MTF-1 FACILITATES REMODELING OF THE TUMOR IMMUNE MICROENVIRONMENT BY REGULATING FERROPTOSIS AND LACTATION MODIFICATIONS IN HEPATOCELLULAR CARCINOMA

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Background: Ferroptosis is an iron-dependent oxidative mechanism of non-apoptotic cell death that has been implicated in regulating the tumor immune microenvironment (TIME). Metal regulatory transcription factor-1 (MTF-1) plays a key role in maintaining iron homeostasis; however, the specific molecular mechanisms involved in this process are unknown.
Methods: The levels of target genes, iron, lactate production, and histone lysine lactylation (Kla) were determined. The interaction between MTF-1 and hepatocyte nuclear factor 6 (HNF6) was confirmed using immunoprecipitation. Cell viability and metastatic ability were evaluated using colony formation, MTT, and Transwell assays, while apoptotic cells were detected by flow cytometry. **Results:** Our data revealed that MTF-1 is closely correlated with ferroptosis in hepatocellular carcinoma (HCC). Overexpressing MTF-1 resulted in glutathione peroxidase 4 upregulation and long chain acyl-CoA synthetase 4 depletion, as well as a low iron level, thereby suppressing ferroptosis. Furthermore, MTF-1 was activated in established sorafenib (a ferroptosis inducer)-resistant HCC cells. MTF-1 interacted with HNF6, which functions as a tumor-suppressor and is involved in glucose metabolism. Silencing of HNF6 promoted HCC development, and led to lactate production that induced lactation modifications of immune cells with elevated Kla levels in the TIME. The characteristic cytokines of M1 macrophages were decreased in HCC tissue, whereas those of M2 macrophages were upregulated, suggesting that the polarization state of tumor-associated macrophages had changed and facilitated TIME remodeling. **Conclusion:** Based on these findings, we hypothesize that the regulation of ferroptosis and lactation modifications by MTF-1 contributes to TIME remodeling and chemotherapy resistance. These results provide the experimental and theoretical basis for targeted HCC therapy and subsequent improved prognosis.

Mo1475

TRANSPLANT FOR INTRAHEPATIC CHOLANGIOCARCINOMA AFTER LIVER-DIRECTED THERAPY, A POTENTIALLY NEW CURATIVE OPTION.

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Background: Intrahepatic cholangiocarcinoma (iCCA) is a relatively rare, but aggressive cancer with poor prognosis (~30% 5-year overall survival). iCCA has long been considered a contraindication to liver transplant in comparison to hilar CCA or hepatocellular carcinoma, which both have well-established United Network for Organ Sharing (UNOS) indications. However, it is unclear whether there are patients with unresectable iCCA who benefit from transplantation. Here, we present our experience with unresectable iCCA who underwent liver-directed therapy with goal of bridging to liver transplant. Methods: Single center, retrospective study of adult patients with unresectable iCCA seen by a transplant hepatologist at Washington University (1/1/20-11/15/23). We excluded patients with very small (<2 cm) tumors or extrahepatic tumors. All patients were evaluated with the intent to offer liver-directed therapy; however, a subset was offered liver-directed therapy with the goal of bridging to transplant after multidisciplinary discussion. On a case-by-case basis, liver-directed therapy with transarterial radioembolization (TARE/Y90), radiofrequency ablation (RFA), or stereotactic body radiation therapy (SBRT) was administered. Chemotherapy was