Modern Outcomes Following Treatment of Hepatocellular Carcinoma in Hereditary Hemochromatosis

A Matched Cohort Study

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Objective: Hepatocellular carcinoma (HCC) is a complication of the common genetic condition hereditary hemochromatosis (HH). It is unknown whether HH as an etiology of liver disease impacts the outcome. We compared the results of liver transplantation (LT), surgical resection and locoregional therapies in a matched cohort study and investigated whether HH as an etiology has an impact on survival.

Materials and Methods: Consecutive patients with HH and HCC (2000 to 2015) were compared with age, sex and Barcelona Clinic Liver Cancer (BCLC) stage-matched non-HH HCC cases. Patients were offered curative or noncurative treatment according to BCLC stage and Milan criteria. The primary endpoint was all-cause mortality.

Results: A total of 102 patients (52 HH; total cohort median age: 67 [44 to 78] y, 97% male, Model for End-stage Liver Disease: 9 [5 to 31]) were studied with a median follow-up of 22 (3 to 126) months. Of the HH cases, the median serum ferritin at diagnosis of HCC was 326 (27 to 5718) μg/L and α-fetoprotein 33 (2 to 197,926) kIU/L. Five-year survival for HH patients receiving curative therapy was 77% (80% for LT, 67% for resection/radiofrequency ablation), and 15% (23% for transarterial chemoembolization) for those undergoing noncurative therapy. Survival for HH patients compared with controls was similar (hazard ratio = 0.949; $P = 0.839$). On multivariate Cox regression survival analysis, BCLC stage, and diagnosis of ischemic heart disease (but not HH diagnosis) were independently associated with reduced survival.

Conclusions: Patients with HCC and HH can achieve comparable survival rates following curative or LRT modalities to other liver diseases. The BCLC staging system accurately stratifies survival and excellent 5-year survival is possible following LT in selected patients.

Key Words: hepatocellular carcinoma, hemochromatosis, liver transplantation, cirrhosis, cancer surgery

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Hereditary hemochromatosis (HH) is an adult-onset, autosomal recessive disorder with a prevalence of ~1 per 250 in whites[1] associated with an inappropriate increase in intestinal iron absorption and, later in life, with increased levels of body iron. The genetic basis was confirmed with the cloning of the HH gene, *HFE* in 1996[2] and the finding that most iron-overloaded individuals were homozygous for the *p*.Cys282Tyr mutation (C282Y). Excess iron deposition in tissues and organs leads to organ dysfunction, with the liver, as the body's largest iron store, being the most susceptible to damage. Excessive iron induces tissue injury and fibrogenesis, which may progress to cirrhosis and hepatocellular carcinoma (HCC) if reduction of iron overload is not undertaken.[3] In studies of clinical outcomes in heavily iron-loaded patients with cirrhosis prior to the identification of *HFE*, a ~200-fold increase in the risk of developing HCC was reported with this diagnosis accounting for 30% to 45% of HH-related deaths.[3–5] In 2 large series, in ~40% of patients, the diagnosis of HH was made retrospectively with iron overload detected as an incidental finding during the investigation of HCC.[5,6] The presence of a high proportion of patients where the index presentation of HH was the diagnosis of HCC means that case series from the pre-genotyping era were dominated by individuals with a poor prognosis and limited treatment options.[5–7]

Following the identification of *HFE*, it became clear that HH was not a highly penetrant disorder. In large population-based surveys, only ~1% of C282Y homozygotes were found to have cirrhosis.[8–10] However, there is a discrepancy between the findings of population screening studies and those from case series of patients referred with a clinical diagnosis of iron overload.[11] Here, referral centers continue to report cirrhosis in 15% of HH patients[12] and in recent series HCC accounted for between 16% and 56% of all-cause mortality.[13–16] Furthermore, in an Italian series in those with cirrhosis, the risk of developing HCC did not differ across 3 decades.[16]

There have been no detailed reports of the modern management of HCC in HH taking in treatment options that now include locoregional therapies.[17] Also, HCC staging systems such as the Barcelona Clinic Liver Cancer Staging System (BCLC) are now widely recognized as an effective strategy for patient stratification,[18,19] calculating severity and prognosis using patient performance status, liver function (Child-Pugh score), tumor size, tumor multiplicity, vascular invasion and the presence of nodal spread, and extrahepatic metastases. Present-day treatment intent is determined by disease severity and performance status but etiology of liver disease does not form part of treatment algorithms.

Liver transplantation (LT) can be offered with curative intent in HCC although historical data series have suggested a survival disadvantage in HH patients after LT, as well as in patients with associated HCC.[20,21] Data extracted from retrospective studies of 5180 LT recipients at 37 centers across the

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United States between 1982 and 1991[20] showed a reduced 1- and 5-year survival in HH patients undergoing LT with figures of 54% and 43% (n = 56), respectively, compared with 79% and 69% survival for the entire patient cohort. Such studies suggest a strong association with reduced posttransplant survival and iron overload. Mortality in these cases was shown to be associated with a higher rate of cardiac complications and atypical, overwhelming infections in patients with HH.[22] However, more recent data from our center suggests that with the appropriate selection this need not be the case and that patient and graft survival figures of 81% and 74% at 1 and 5 years respectively can be achieved.[23] Whether this is also true for other therapy modalities in HH patients with HCC is not clear.

As late-presenting HCC continues to present a perceived therapeutic challenge in HH we undertook this retrospective cohort study in our center to assess whether HH as an etiology has an impact on HCC survival rates across the BCLC grades.

MATERIALS AND METHODS

Patient Data

Consecutive patients (n = 52) with HH and HCC diagnosed between 2000 and 2015 at our institution were identified from a prospectively maintained database. A control set of 50 patients with alcohol-related and non–alcohol-related fatty liver disease (ARLD and NAFLD) were sourced from the same database matched for age, sex, tumor multiplicity, aims of therapy (curative or not), and BCLC stage at diagnosis. Patients with active viral hepatitis (due to evolution in antiviral medications) were excluded from the control cohort.

HH was diagnosed using European Association for Study of the Liver (EASL) guidelines[24] and iron stores removed as discussed below. Patients with increased body iron stores were evidenced by elevated serum ferritin (SF, > 200 μg/L in premenopausal women, > 300 μg/L in men/postmenopausal women) and increased transferrin saturation (> 45%) with confirmatory genetic testing for C282Y homozygosity. Liver biopsy was offered to patients with SF > 1000 μg/L, hepatomegaly, high serum aspartate transaminase or over 40 years of age to assess the degree of iron overload and grade of fibrosis. Testing for diabetes, joint disease, hypothyroidism, osteoporosis or cardiac disease was undertaken. Cirrhosis was defined by at least 2 compatible diagnostic tests from the following: liver biopsy (fibrosis grade ≥ 5), radiologic (ultrasound [US], computed tomography [CT], or magnetic resonance imaging [MRI]), clinical (presence of hepatocellular jaundice/ascites/hepatic encephalopathy), or biochemical (hyperbilirubinemia, prolonged prothrombin time, and/or thrombocytopenia).

Iron stores were removed by phlebotomy initially every 1 to 2 weeks and then with a lower frequency as SF normalized.

HCC was diagnosed and treatment planned by multidisciplinary assessment using EASL guidelines,[25] based on 2 imaging modalities consistent with HCC (usually USs and CT and/or MRI) with α-fetoprotein (AFP) used as a surrogate marker of both diagnosis and response to therapy in those patients who secreted AFP. CT diagnostic criteria included lesion enhancement in the arterial phase and subsequent washout in portal venous/delayed phases. Dynamic contrast-enhanced MRI was used in cases of diagnostic doubt or to avoid repeated radiation dosing. Unifocal lesions <1 cm in diameter were treated as indeterminate and underwent interval radiologic follow-up. Lesional biopsy preadjunct radiofrequency ablation (RFA) was used in a minority of cases. Prognostic measures calculated included the Child-Pugh grade at diagnosis,[26] Model for End-stage Liver Disease (MELD),[27] and BCLC[18] stage and patients were followed until the primary endpoint of all-cause mortality. All patients underwent multidisciplinary assessment for diagnosis and therapeutic planning. Abstinence from alcohol was required for 6 months pre LT for those where alcohol was deemed to be a cofactor and treatment of hepatitis C infection was undertaken if safe to do so. However, this cohort dates primarily from before the introduction of direct-acting antivirals. All data collection and analysis was undertaken in accordance with the Declaration of Helsinki.

Radiologic Interventions

RFA was performed in patients with solitary HCC <2 cm or following transarterial chemoembolization (TACE) in larger tumors (2 to 3 cm). TACE was delivered under angiographic guidance following arterial puncture to BCLC-A/B patients without significant hepatic decompensation, or those not fulfilling criteria for surgical resection or RFA. TACE was also used as a bridge to LT in those predicted to wait > 3 months for a donor liver. Doxorubicin and lipiodol were used and therapeutic effect evaluated using standard criteria for lipiodol deposition with reduction or loss of arterialization on CT. In the minority bland embolization without chemotherapy was employed in cases of multiple previous doses of doxorubicin or concerns regarding cardiac dysfunction. Whole-body cross-sectional imaging was performed at 6-weeks postintervention to assess therapeutic response. If no further treatment was required, the surveillance continued at 3 monthly intervals thereafter for 2 years, then 6 monthly for 3 years, finally transferring to 6 monthly liver USs. Further therapy was guided by the oncological response and clinical assessment regarding decompensation and BCLC restaging.

Surgical Interventions

Milan criteria were used as transplant listing criteria as per UK policy.[28] Immunosuppression routinely involved calcineurin inhibition with tacrolimus and tapered corticosteroids. Mycophenolate mofetil was added in cases of failure to control suspected or biopsy-proven T-cell–mediated acute rejection at maximal tacrolimus dosing, or where dose reduction in the primary immunosuppressant due to toxicity was required. The minimum doses to prevent rejection were used to reduce the recurrence risk, conversion to mammalian target of rapamycin-inhibition–based immunosuppression was on an individual patient basis.

Chemotherapy and Palliative Care

The tyrosine kinase inhibitor sorafenib was not available in the United Kingdom until the latter part of this study, so for patients without curative, locoregional or chemotherapeutic options this agent began to be available in 2007 and was more widely used from 2011. Palliative care was coordinated from within the multidisciplinary team by cancer nurse specialists, primary care and cancer-specific charitable services.

Statistical Methods

Continuous data were reported as median (range) or mean (SD) contingent on normality testing. Between-group comparisons were made using the χ^2 test for categorical variables or Mann-Whitney *U* test for nonparametric continuous data. Survival analysis was by Kaplan-Meier analysis and Cox hazards regression reporting hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariate methods were performed using backward Cox regression with an initial *P*-value rejection threshold of 0.2. Statistical significance was defined at the 95% level ($P < 0.05$). Case wise deletion was used for missing data.

Data were analyzed using MedCalc, v 17 software (MedCalc Software, Mariakerke, Belgium).

RESULTS

Cohort Characteristics

The HH cohort comprised 52 patients (all C282Y homozygous, median [range] age: 67 [44 to 84] y, 98% male) with a median follow-up of 30 (95% CI: 17-40) months. A further 50 patients made up the control cohort (30 ARLD, 17 NAFLD, 3 cryptogenic cirrhosis, Table 1). Two patients were lost to follow-up to other hospitals at 6 and 12 months, respectively. In addition to the diagnosis of HH, 9 patients were deemed to have ARLD as a cofactor to the cause of cirrhosis, 2 had NAFLD and 1 patient genotype 3a chronic hepatitis C infection.

The metabolic or cardiovascular disease was the commonest comorbidities in the HH group with 23 (44%) patients with diabetes mellitus, 15 (29%) patients with systemic arterial hypertension, but only 2 (4%) with cerebrovascular disease manifesting as stroke and 5 (10%) with proven ischemic heart disease. Seven patients had atrial fibrillation. Extrahepatic malignancy was diagnosed in 5 patients during follow-up; bronchial adenocarcinoma (1), Duke C adenocarcinoma of the colon (1), prostate cancer (1), and renal cell carcinoma (2).

Median MELD score in HH patients at the time of diagnosis was 8 (5 to 31). Forty-five (87%) patients had cirrhosis. The median SF at presentation with HCC was 326 (27 to 5718) and median serum AFP 33 (2 to 197,926) kIU/L.

TABLE 1. Characteristics at Baseline (Diagnosis of Hepatocellular Carcinoma) For This Cohort of Patients With HH and Hepatocellular Carcinoma and Non-HH Controls

Variables	Cases (HH)	Controls (Non-HH)	*P*
	52	50	
Age (y)	67 (44-84)	66 (45-83)	0.859
Sex (male:female)	51:1	48:2	0.536
Cirrhosis (yes:no)	45:7	47:3	0.207
BCLC stage (A:B:C:D)	25:12:14:2	23:17:7:3	0.334
Tumor diameter (dominant/cm)	4 (1.1-27)	4 (1.4-12)	0.543
Unifocal (yes:no)	30:22	21:29	0.114
α-Fetoprotein (IU/L)	33 (2-197,926)	50 (2-101,323)	0.453
Aspartate transaminase (IU/L)	58 (19-180)	55 (13-303)	0.652
Bilirubin (μmol/L)	16 (6-477)	25 (5-290)	0.120
GGT (IU/L)	124 (22-957)	243 (21-944)	0.642
Ferritin (μg/L)	326 (27-5718)	101 (8-2266)	0.006
TIBC (μmol/L)	47 (25-71)	—	—
Sodium (mmol/L)	139 (125-145)	138 (110-144)	0.281
Creatinine (μmol/L)	84 (44-137)	80 (49-215)	0.575
Urea (mmol/L)	4.9 (2.7-12)	5.7 (2-15)	0.100
INR	1.1 (0.9-2.7)	1.2 (0.9-1.9)	0.125
White cell count ($\times 10^9$/L)	6.2 (2.6-12.6)	7.0 (2.5-13.9)	0.407
Hemoglobin (g/dL)	142 (90-171)	121 (74-170)	<0.001
Platelets ($\times 10^9$/L)	175 (26-543)	171 (39-632)	0.696
Albumin (g/L)	41 (20-48)	36 (21-49)	0.004
MELD	8 (5-31)	10 (5-21)	0.304
Child-Pugh Score	6 (5-15)	7 (5-12)	0.245
Diabetes mellitus (yes:no)	23:29	18:22	0.300
Hypertension (yes:no)	15:37	18:32	0.442
Ischemic heart disease (y)	5:47	10:40	0.276
Year of diagnosis	2008 (2000-2016)	2009 (2000-2015)	0.725

Continuous variables are described by the median (range).

Calculation of *P*-values was performed using the χ^2 test for categorical variables and Mann-Whitney *U* test for continuous variables.

BCLC indicates Barcelona Clinic Liver Cancer; GGT, γ-glutamyl transferase; HH, hereditary hemochromatosis; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; TIBC, total iron-binding capacity.

Tumor and Staging Characteristics

Thirty (58%) HH patients had solitary tumors, whereas 7 (14%) and 4 (9%) had 2 and 3 tumors, respectively. The remaining 9 (18%) patients had 4 tumors or diffuse HCC. Seven patients (14%) required lesional biopsies due to non-diagnostic radiologic features and low AFP levels. At the time of diagnosis of HCC 44% of patients were BCLC stage A, 27% BCLC-B, 10% BCLC-C, and 5% BCLC-D.

The matched control cohort comprised of 50 patients with HCC on the background of chronic ARLD or NAFLD and were matched for all major demographic, tumor, extrahepatic comorbidity and liver function-related parameters except for hemoglobin, ferritin, and albumin concentrations.

Treatments

In terms of treatment with curative intent in the HH group, 5 patients (10%) underwent surgical resection in the form of right posterior sectionectomy (1), left lateral segmentectomy (1), and wedge resection (3). One patient developed a bile leak following resection managed conservatively. RFA was performed in 5 (12%) patients and in 4 as adjunctive therapy. Fourteen patients (27%) underwent LT. TACE was the commonest locoregional therapy in 25 (50%) patients with 14 (27%) patients receiving a second embolization and 2 patients receiving 3 or such treatments. Most patients were treated before the introduction of sorafenib into United Kingdom practice, but 3 patients received sorafenib in this cohort.

Survival

Eleven patients had new disease after effective treatment of the initial tumor and in 3 patients this was following LT, 6 following TACE (1 as a bridge to LT), 1 post-RFA, and 2 following surgical resection. The site of new disease was hepatic in 7 (64%) and extrahepatic (lung, bone, and adrenal) in the remainder. The median time to de novo disease was 15 months.

Median overall survival was 30 (95% CI: 17-41) months. Patients with >1 HCC did not have decreased survival compared with those with a single tumor ($P = 0.315$). Five-year survival for patients receiving LT was 80% and 21% for those undergoing resection ($P < 0.001$). Median survival in the non-LT group was 21 months. In patients receiving TACE 1-, 2-, and 3-year survival was 81%, 64%, and 52%, respectively. For BCLC-A and B patients' median survival was not attained, and for BCLC-C/D patients 8 (95% CI: 6-20) months, $P = 0.002$, log-rank test. Compared with non-HH controls overall survival was not affected by the presence of HH as an etiological factor on Kaplan-Meier analysis (HR = 1.06; 95% CI: 0.590-1.894, $P = 0.839$) (Figs. 1A–D).

Regression Analysis

Univariate regression using the whole cohort identified tumor diameter and BCLC stage as statistically significant hazards for mortality. Hematological features associated with a higher risk of death were leukocyte and platelet count. MELD or its constituent biochemical parameters were not associated with mortality.

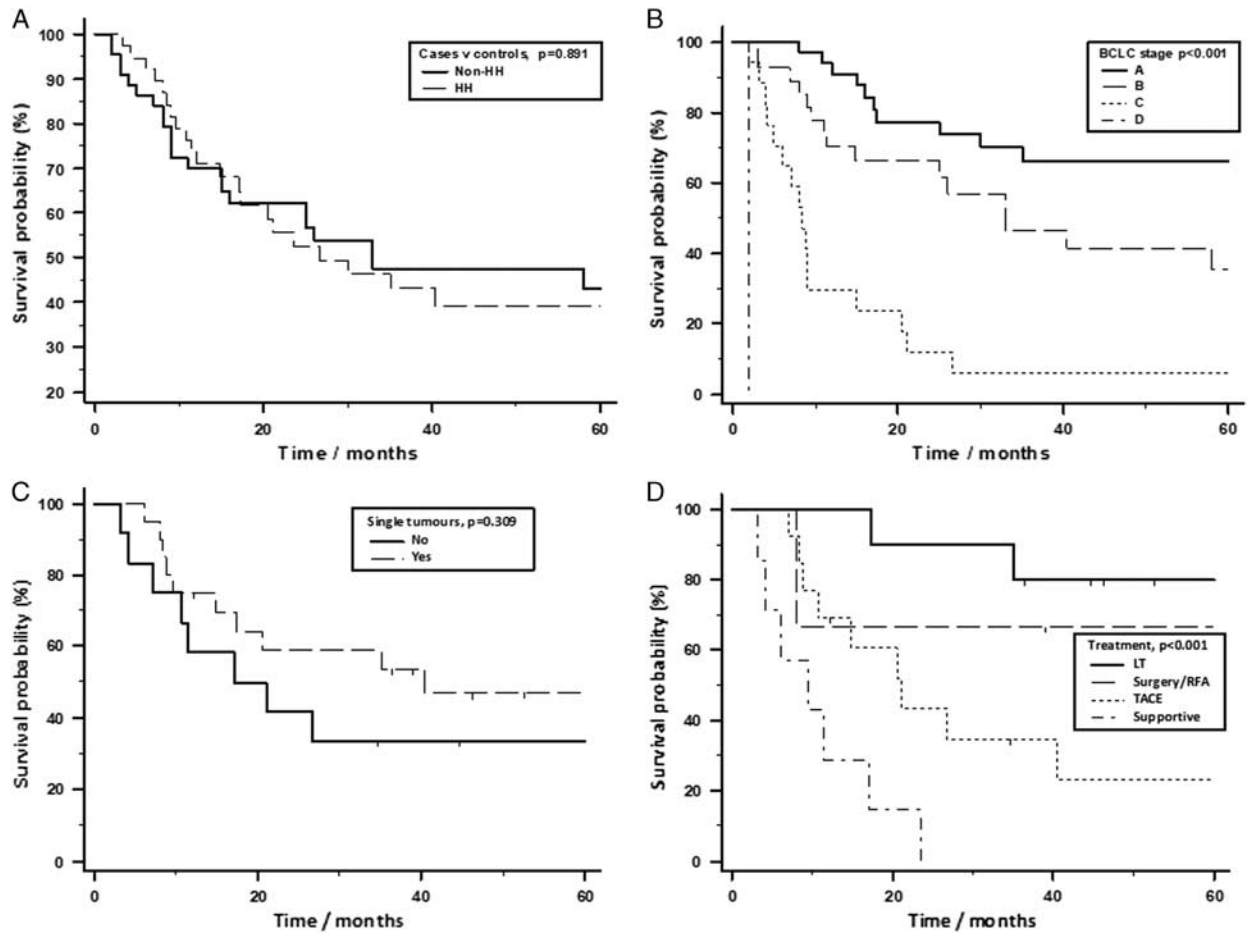

FIGURE 1. A, Kaplan-Meier (KM) analysis for all-cause mortality comparing patients with hepatocellular carcinoma (HCC) and hereditary hemochromatosis (HH) versus non-HH controls. B, KM curves for all-cause mortality as per Barcelona Clinic Liver Cancer (BCLC) stage at diagnosis. C, KM curves for all-cause mortality in patients with HCC and HH in this cohort divided into whether they had the unifocal or multifocal disease at the time of diagnosis of HCC. D, KM curves divided into treatment modality from the time of diagnosis of HCC (cases of adjunct radiofrequency ablation [RFA] were included in the transarterial chemoembolization [TACE] group and RFA with initial curative intent in the surgery/RFA group). For all—censored data marked in graph. LT indicates liver transplantation.

Serum AFP, SF, and the presence of cirrhosis were not independently associated with long-term mortality. On Kaplan-Meier analysis a difference in long-term survival was only detected at BCLC stage C compared with A and so stages were dichotomized to A/B versus C/D for subsequent Cox regression. In a backward selection model diagnosis of ischemic heart disease (HR = 2.6; 95% CI: 1.1-6.1, $P = 0.023$) and BCLC stage C/D (HR = 9.5; 95% CI: 4.6-19.6, $P < 0.001$, overall model: $P < 0.001$) were independently associated with mortality. Tumor diameter was collinear with BCLC stage and therefore not explicitly entered in the model and white cell count and platelet count were also not retained in the model.

HH as an etiology was not associated with increased risk of death (Table 2).

DISCUSSION

This study demonstrates that in patients with HCC, HH was not associated with an increased risk of mortality compared with non-HH controls following therapeutic intervention. HCC in the context of HH can be successfully prognosticated and treated using modern modalities to achieve cure and palliation. Previous dogma regarding prognostic pessimism for patients with HCC and HH should be challenged.

We found the dominant determinant of long-term survival to be BCLC stage at diagnosis. Interestingly low SF at the time of diagnosis was not associated with any survival benefit. Many patients were already undergoing venesection before HCC diagnosis which confounds the effect of intrahepatic iron levels on tumor initiation and progression. SF at the time of HH diagnosis (pre-venesection) is likely to reflect long-term hepatic iron burden more accurately and hepatic iron is well described as highly prooncotic.

Our median survival rate compared favorably to patients with HCC without HH. A 30% 5-year survival rate is noted in registry data.[29] Our 5-year survival rate is comparable (40% for HH patients, falling to 21% following the exclusion of LT recipients). Conversely, 5-year survival rates of 70% are expected for patients with HCC following LT and we exceeded this. This may reflect the more recent reporting of our cohort given the ongoing improvements in survival following elective LT.

Surgical resection was only offered to the minority of cases because many cases of HCC occurred on the background of cirrhosis with portal hypertension. Nevertheless, the excellent 5-year survival of 64% in patients treated with curative

TABLE 2. Univariate and Multivariate Cox Regression Analysis For Determinants of Survival in Patients With Hepatocellular Carcinoma and HH and Controls

	Univariate			Multivariate		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	1.024	0.968-1.083	0.407			
HH	0.949	0.526-1.683	0.839			
BCLC stage						
A/B	1			1		
C/D	5.458	1.827-16.37	0.002	9.450	4.56-19.61	< 0.001
Cirrhosis	0.811	0.187-3.522	0.783			
Curative intent	0.147	0.042-0.519	0.003			
Tumor diameter (dominant)	1.219	1.094-1.358	< 0.001			
Unifocal (yes:no)	0.619	0.243-1.575	0.314			
α-Fetoprotein (IU/L)*	1.074	0.933-1.123	0.314			
Asparate transaminase (IU/L)	0.995	0.987-1.011	0.931			
Bilirubin (μmol/L)	0.997	0.991-1.004	0.558			
GGT (IU/L)	1.001	0.999-1.003	0.062			
Ferritin (μg/L)	1.000	0.999-1.000	0.440			
TIBC (μmol/L)	1.057	0.953-1.173	0.290			
Sodium (mmol/L)	1.023	0.922-1.137	0.658			
Creatinine (μmol/L)	0.996	0.975-1.019	0.781			
Urea (mmol/L)	1.000	0.763-1.308	0.999			
INR	0.982	0.324-2.972	0.974			
White cell count ($\times 10^9$/L)	1.500	1.150-1.956	0.002			
Hemoglobin (g/dL)	1.032	0.993-1.072	0.107			
Platelets ($\times 10^9$/L)	1.004	1.000-1.008	0.041			
Albumin (g/L)	1.029	0.954-1.110	0.455			
MELD	1.003	0.939-1.071	0.919			
Child-Pugh Score	0.929	0.729-1.167	0.502			
Diabetes mellitus (yes:no)	0.602	0.238-1.612	0.327			
Hypertension (yes:no)	0.664	0.245-1.801	0.422			
Ischemic heart disease (yes:no)	4.030	1.059-15.32	0.040	2.59	1.16-6.09	0.028
Alcohol cofactor	0.730	1.681-3.173	0.674			
Year of diagnosis	1.036	0.965-1.102	0.357			

The presence of HH as an etiological factor was not associated with an increased risk of long-term mortality.

*Log-transformed variable.

BCLC indicates Barcelona Clinic Liver Cancer; CI, confidence interval; GGT, γ-glutamyl transferase; HH, hereditary hemochromatosis; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; OR, odds ratio; TIBC, total iron-binding capacity.

Overall multivariate model: $P < 0.001$.

intent is in keeping with those quoted by other centers for non-HH cases.[18] Therefore, in patients with HH and controlled iron overload, curative treatment options should be encouraged despite reported underutilization.[30]

TACE was used in 25 HH patients, once as a bridge to LT and for 50% of patients, a further TACE session was provided due to recurrence/incomplete response. Drug-eluting beads (DEB-TACE) were only used in 2 cases as it became available at out institution. The effect of this modality on survival is not well known in HH cases and should be prospectively evaluated, given the desirability of reduced cardiac complications.[31]

Sorafenib was also only available for the latter part of this study and hence most patients did not receive sorafenib. Whether sorafenib-induced ferroptosis[32,33] demonstrates a significant response in patients with HH and HCC beyond case reports remains unknown.[34]

The limitations of this study include its small size and single-center design and warrants validation from centers where LT is not readily available. However, these data represent a unique analysis of outcomes of patients with HCC and HH managed with modern locoregional and surgical therapy. Given the higher risk of HCC in this etiology of chronic liver disease, these data are important to inform modern management.

In summary, this matched cohorts represents a unique analysis of survival of HCC and HH managed with modern locoregional and surgical therapy. Patients with HCC and HH benefit from tailored multimodality treatment, producing survival comparable to patients without HH. Therefore, prognostic pessimism in HH with HCC is not warranted.

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