Original Article

Promising role of liver transplantation in patients with combined hepatocellular-cholangiocarcinoma: a propensity score matching analysis

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Background: Combined hepatocellular-cholangiocarcinoma (CHC) is a rare but vital heterogeneous histological subtype of primary liver cancer (PLC) with no standardized treatment strategy. This study aimed to preliminarily investigate the role of liver transplantation (LT) in CHC and develop a novel risk scoring model (RSM) to evaluate the benefits of transplantation.

Methods: The study cohort was taken from the Surveillance, Epidemiology, and End Results database. The annual percent change (APC) in incidence or ratio was calculated utilizing the Joinpoint regression. Propensity score matching (PSM) was introduced to reduce the selection bias between groups. A novel RSM was developed based on the independent prognostic factors identified by the Cox regression model. The predictive performance of the RSM was compared with the Milan Criteria and the University of California, San Francisco (UCSF) Criteria, respectively.

Results: A total of 223 CHC patients were enrolled, and 60 (26.9%) of them received LT. The incidence-based mortality did not decrease between 2004 and 2015 (APC =1.7%, P=0.195). Although LT was considered an independent protective predictor for CHC, it showed a declining ratio from 33.3% in 2004 to 15.4% in 2015 (APC =–8.9%, P=0.012). The LT recipients had better outcomes than others who underwent hepatectomy or local destruction (P<0.05). Compared with other subtypes of PLC, the post-transplantation prognoses of CHC patients were similar to those with hepatocellular carcinoma (P>0.05) but significantly better than those with intrahepatic cholangiocarcinoma (ICC) (P<0.05). Based on the RSM (vascular invasion: 1 point; tumor size >2 cm: 1 point; multiple tumors: 2 points), patients were stratified into two prognostic subgroups: the low-risk (scoring ≤2) and the high-risk (scoring >2 or extrahepatic metastasis) groups. Patients in the low-risk group were more likely to benefit from LT. The predictive performance of the RSM outperformed the Milan and UCSF Criteria in both the training and validation sets.

Conclusions: Therapeutic strategies for CHC should be further improved. Patients with CHC should also be considered potential LT candidates. The novel RSM could be helpful to stratify patients and assist clinical decision-making.

Keywords: Combined hepatocellular-cholangiocarcinoma (CHC); liver transplantation (LT); propensity score matching (PSM); risk scoring model (RSM); the Surveillance, Epidemiology, and End Results program (the SEER program)

Submitted Oct 11, 2021. Accepted for publication Jan 28, 2022.
doi: 10.21037/atm-21-5391
View this article at: https://dx.doi.org/10.21037/atm-21-5391

Introduction

Combined hepatocellular-cholangiocarcinoma (CHC) is a rare histological subtype of primary liver cancer (PLC), accounting for 0.4–14.2% of all PLCs (1-10). According to the World Health Organization (WHO) classification of tumors of the digestive system (5th edition), CHC is defined as PLC with both hepatocellular and cholangiocytic differentiation in the same tumor, which is consistent with the type 3 tumor proposed by Allen and Lisa (11) and the type 2 tumor described by Goodman *et al.* (12). Due to its complexity, CHC exhibits mixed clinicopathological characteristics from hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), creating challenges for diagnosis and clinical decision-making (4,13-16).

In contrast to HCC and ICC, the treatment of CHC is not yet standardized. Overall, surgery remains the cornerstone, including 3 main surgical approaches: hepatectomy (Hx), local destruction (LD), and liver transplantation (LT) (4,5,7-9). Although LT has been considered a standard treatment for HCC, it is traditionally recognized as a relative contraindication for CHC patients on account of the ICC component. Only a few CHC patients receive LT mainly due to misdiagnosis of HCC (17-23). In addition, the current American Joint Committee on Cancer (AJCC) staging system (8th edition) classifies CHC and ICC into the same category. However, many studies have pointed out sufficient differences between the 2 cancers, indicating that CHC should be considered a separate entity to be evaluated independently (14,24-27). Therefore, several researchers have refocused on the therapeutic value of LT in CHC patients and obtained some contradictory results (18,19,28-32). Given these circumstances, we aimed to utilize a large-scaled population-based database to explore the role of LT and develop a risk scoring model (RSM) to evaluate the benefits of LT in CHC patients. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5391/rc).

Methods

Patients

This study was a retrospective cohort study. Clinicopathological data of patients with PLC (ICD-O-3 Histology Code =8160/3, 8170/3 and 8180/3) from 2004 to 2015 were extracted from the Surveillance, Epidemiology, and End Results (SEER) Research Database (18 Registries). Data were downloaded with SEER*Stat software (version 8.3.9; The SEER Program, https://seer.cancer.gov). The criteria were shown as follows: (I) age ≥18 years old; (II) diagnosed as PLC with positive histology; (III) surgery performed and known surgical approach; (IV) primary tumor could be assessed; and (V) known cause of death and survival time ≥1 month. The stepwise extraction process from the SEER database is shown in *Figure 1*.

This study was conducted in accordance with the tenets of the Declaration of Helsinki (as revised in 2013). The SEER database is a public database without personal identifying information. In this context, the ethical review was exempted, and no consent was needed in this study.

Definition

Morbidity and incidence-based mortality (IBM) were calculated in pathologically confirmed adult patients and age-adjusted to the 2000 US standard population. For a given year, IBM is the proportion of the total number of deaths attributed to CHC in that year. Attribution to CHC is made when the cause of death is CHC, and the deceased is listed in the registry as having been previously diagnosed with CHC (33). Annual percentage change (APC) was utilized to describe trends of incidence and ratio. Overall survival (OS) was defined as the time from diagnosis until death from any cause or the most recent follow-up. Cancer-specific survival (CSS) was defined as the time from diagnosis until death caused by CHC or the most recent follow-up. We set OS and CSS as the primary outcomes of this study. All patients were restaged to the 8th edition AJCC

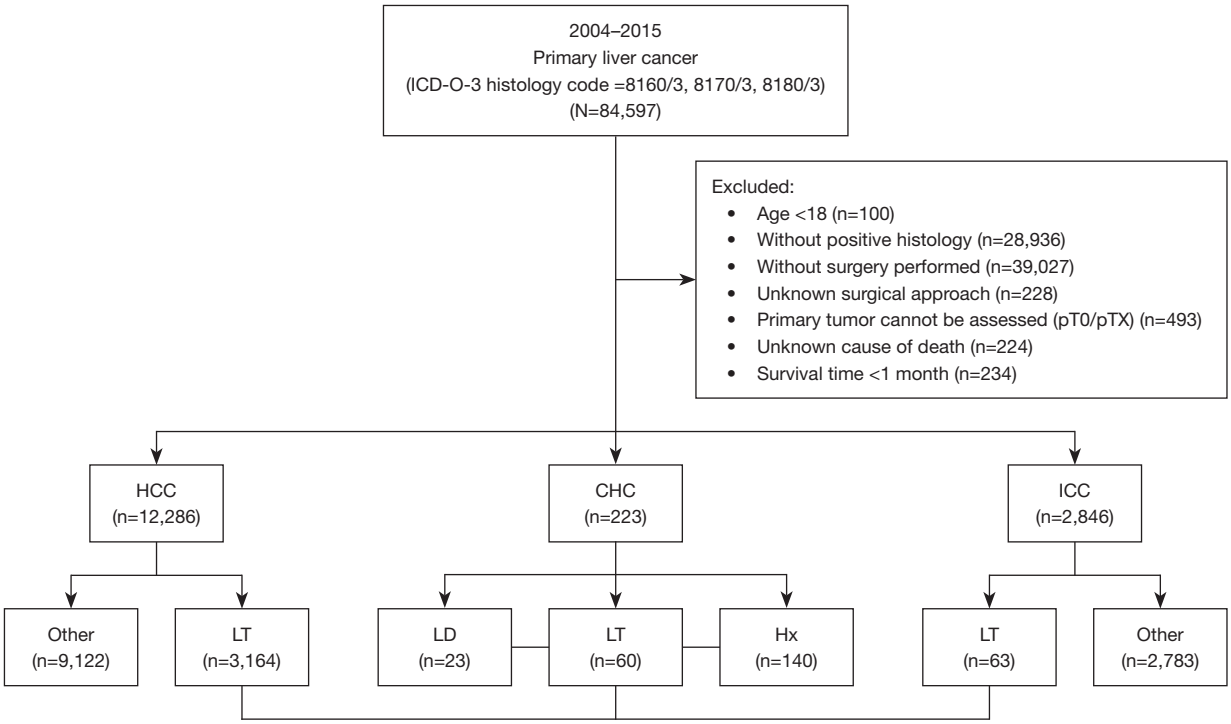

Figure 1 Stepwise extraction process from the Surveillance, Epidemiology, and End Results database. CHC, combined hepatocellular-cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; Hx, hepatectomy; LD, local destruction; LT, liver transplantation.

staging system based on the specific fields in the SEER database.

Statistical analysis

With the hypothesis that the incidence and ratio changed at a constant percentage from the previous year, the curve was fitted using the Joinpoint Regression Program software (version 4.7.0; IMS, Inc., Calverton, MD, USA) (34). Survival curves were plotted with the Kaplan-Meier method and compared by the log-rank test. Survival analyses were performed by the Cox regression model, and β regression coefficient, hazard ratio (HR), and 95% confidence interval (CI) were calculated. Categorical variables were shown as numbers and compared using the chi-square test or Fisher's exact test. Propensity score matching (PSM) was used to reduce selection bias, and a one-to-one match was performed by the nearest-neighbor method between the 2 groups.

Patients with CHC who underwent LT were randomly divided into a training and validation set with the ratio of 1:1 for external validation. A RSM was constructed based on the independent variable weighted by the β regression coefficient. Akaike information criterion (AIC), Bayesian information criterion (BIC), Harrell's C-index, and area under receiver operating curves (AUROC) were calculated to compare prognostic performances. Analysis of variance (ANOVA) analyses were applied to assess the statistical significance of different models. A result was considered statistically significant when two-tailed $P<0.05$. All statistical analyses were completed using R software (version 3.6.3; The R Foundation for Statistical Computing, http://www.r-project.org).

Results

Morbidity and incidence-based mortality of CHC between 2004 and 2015

The overall incidence of CHC seemed to have an increasing trend with a borderline P value (P=0.060). The morbidity was 0.623 per 1 million individuals in 2004 and 0.660 per 1 million individuals in 2015 with an APC of 2.1% (95% CI: −0.1% to 4.3%, *Figure 2A*). Data were further examined

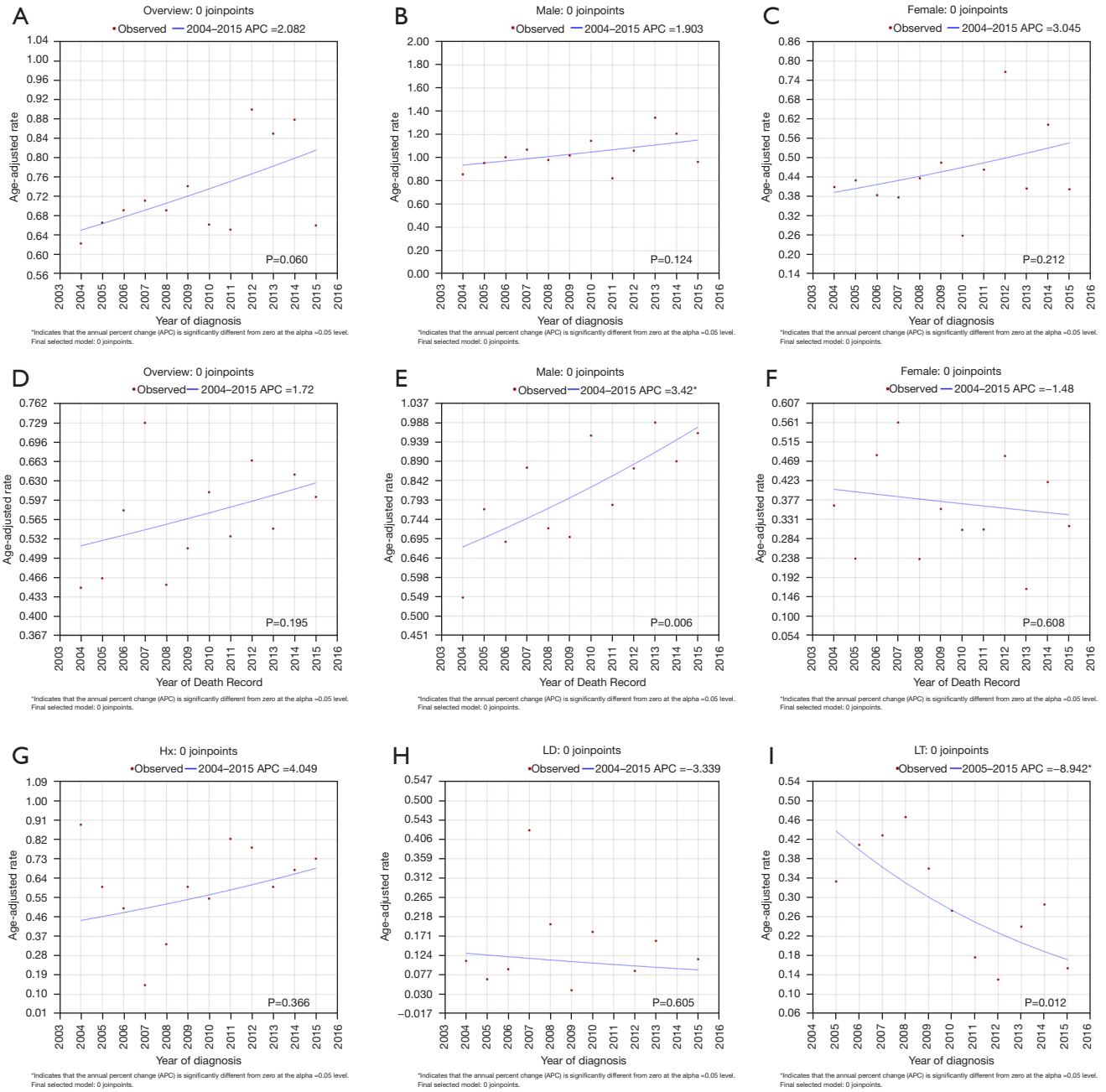

Figure 2 The variation trends and APC values from 2004 to 2015 for (A-C) the morbidity of CHC displayed in the order of overview, male and female; (D-F) the incidence-based mortality of CHC displayed in the order of overview, male and female; (G-I) the ratio of different surgical approaches displayed in the order of Hx, LD and LT. APC, annual percent change; CHC, combined hepatocellular-cholangiocarcinoma; Hx, hepatectomy; LD, local destruction; LT, liver transplantation.

according to gender. The morbidity of CHC in males was 0.857 per 1 million individuals in 2004 and 0.964 per 1 million individuals in 2015, and the APC was 1.9% (95% CI: −0.6% to 4.5%, P=0.124, *Figure 2B*). As for females, the incidence was 0.409 per 1 million individuals in 2004 and 0.402 per 1 million individuals in 2015, and the APC was 3.0% (95% CI: −2.0% to 8.3%, P=0.212, *Figure 2C*). The morbidity of CHC was obviously male dominated, with a

gender ratio of approximately 2:1.

The overall IBM of CHC remained stable between 2004 and 2015, and it was 0.449 per 1 million individuals in 2004 and 0.603 per 1 million individuals in 2015, with an APC of 1.7% (95% CI: −1.0% to 4.5%, P=0.195, *Figure 2D*). However, the IBM continued to increase in males, with an APC of 3.4% (95% CI: 1.2% to 5.7%, P=0.006, *Figure 2E*). For females, the IBM did not change much between 2004 and 2015. The APC value was −1.5% (95% CI: −7.5% to 4.9%, P=0.608, *Figure 2F*).

Baseline characteristics and survival analyses of CHC patients

The baseline characteristics and survival analyses of CHC patients are shown in Table S1. A total of 223 CHC patients were enrolled, comprising 68 (30.5%) females and 155 (69.5%) males. The median age was 60 [interquartile range (IQR): 54, 67] years old. More than one-third (35.9%) of CHC patients had tumors greater than 5 cm in diameter. According to the latest AJCC staging system, there were 94 (42.2%), 114 (51.1%), 6 (2.7%), and 9 (4.0%) patients categorized into the T1, T2, T3, and T4 stages, respectively. Lymph node metastasis (N1) was identified in 17 (7.6%) cases. A total of 12 (5.4%) cases were reported to have distant metastasis (M1). Most patients (53.3%, 60/169) with known clinical data had poorly differentiated or undifferentiated tumors. It was revealed that Hx, LD, and LT were performed in 140 (62.8%), 23 (10.3%), and 60 (26.9%) patients, respectively. As shown in *Figure 2G-2I*, the ratio of Hx and LD held steady during 2004 and 2015. However, the ratio of LT declined gradually: it was 33.3% in 2004 and 15.4% in 2015, with an APC of −8.9% (95% CI: −14.9% to 2.6%, P=0.012).

The final follow-up was performed in November 2020, with a median follow-up time of 33.0 (IQR: 12, 62) months. During the period, a total of 144 (64.6%) patients had died. The median OS was 34.0 (95% CI: 21.1–46.9) months, and the median CSS was 54.0 (95% CI: 21.4–86.6) months. The 1-, 3- and 5-yr OS were 74.9%, 48.1%, and 39.2%, respectively. The 1-, 3- and 5-yr CSS were 79.2%, 53.7%, and 46.5%, respectively. According to multivariate survival analyses, surgery was an independent prognostic factor for both OS and CSS (P<0.05, Table S1).

The therapeutic value of LT in CHC patients

The baseline characteristics of CHC patients receiving LT, Hx, and LD are shown in Table S2. As displayed in *Figure 3A,3B*, the 1-, 3-, 5-yr OS and 1-, 3-, and 5-yr CSS of patients with LT were 86.7%, 68.3%, 56.6% and 89.7%, 74.1%, 65.3%, respectively. Cases who underwent LT showed significantly better outcomes than those who received Hx and LD (both P<0.001). To reduce the selection bias caused by surgical indications, PSM analyses were performed. After matching, LT could still bring better survival benefits to CHC patients compared with Hx (P<0.05, *Figure 3C,3D*, Table S3). The 5-yr OS and 5-yr CSS were 62.8% and 73.1% in the LT group and 38.6% and 45.2% in the Hx group, respectively. The same results were also obtained from the comparisons between LT and LD in CHC patients after PSM (P<0.05, *Figure 3E,3F*, Table S4). The 5-yr OS and 5-yr CSS were 62.3% and 49.2% in the LT group and 26.7% and 16.3% in the LD group, respectively.

Furthermore, horizontal comparisons were conducted among different subtypes of PLC. The baseline characteristics of LT recipients who had been diagnosed with CHC, HCC, and ICC are displayed in Table S5. The intermediate prognoses of LT recipients with CHC compared to those with HCC and ICC are shown in *Figure 4A,4B* (P<0.001). However, after matching, patients with CHC and HCC shared similar outcomes after LT (P>0.05, *Figure 4C,4D*, Table S6). Recipients with CHC still showed better survival than those with ICC (P<0.05, *Figure 4E,4F*, Table S7). The 5-yr OS and 5-yr CSS were 57.9% and 70.6% in CHC patients and 42.2% and 47.2% in ICC patients, respectively.

Development and validation of the RSM to predict prognoses of LT recipients with CHC

To construct a RSM to predict survival, further survival analyses were performed in 60 CHC patients who received LT. The study patients were randomly divided into the training and validation set with a ratio of 1:1. The baseline characteristics of the 2 sets are displayed in Table S8. Based on multivariate survival analyses, multiple tumors, tumor size >2 cm, and vascular invasion were confirmed as the independent prognostic indications of both OS and CSS in the training set (all P<0.05, Table S9). Therefore, these 3 variables were selected to develop the RSM, and the β coefficients derived from the Cox regression model were transformed into relative points listed in *Table 1*. With the aim of acquiring a quick prognostic evaluation of LT recipients with CHC in clinical use, these cases

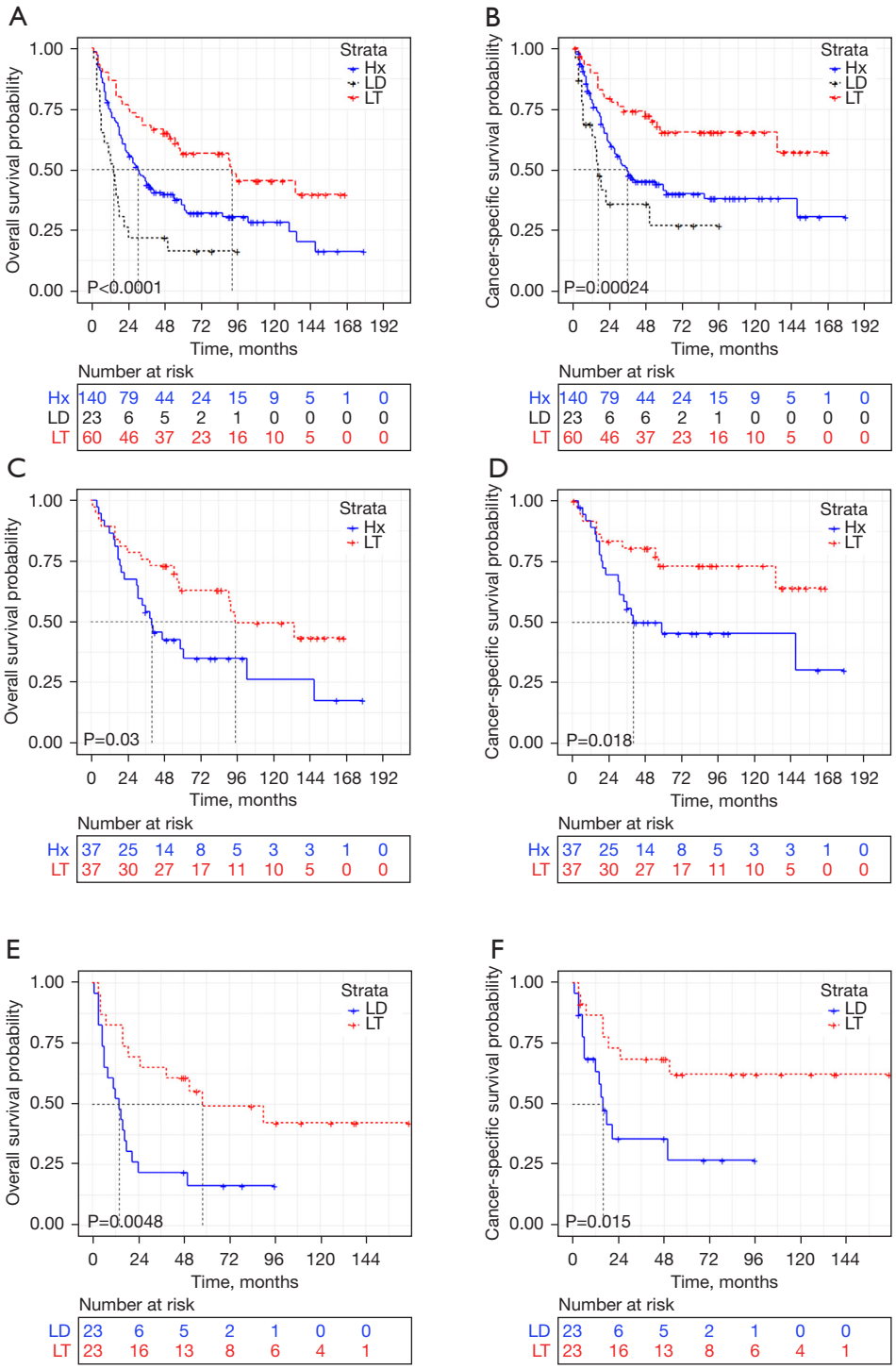

Figure 3 Kaplan-Meier survival analyses of overall survival and cancer-specific survival in CHC patients according to different surgical approaches. (A,B) Hx *vs.* LD *vs.* LT in all patients; (C,D) Hx *vs.* LT in selected patients after PSM; (E,F) LD *vs.* LT in selected patients after PSM. CHC, combined hepatocellular-cholangiocarcinoma; Hx, hepatectomy; LD, local destruction; LT, liver transplantation; PSM, propensity score matching.

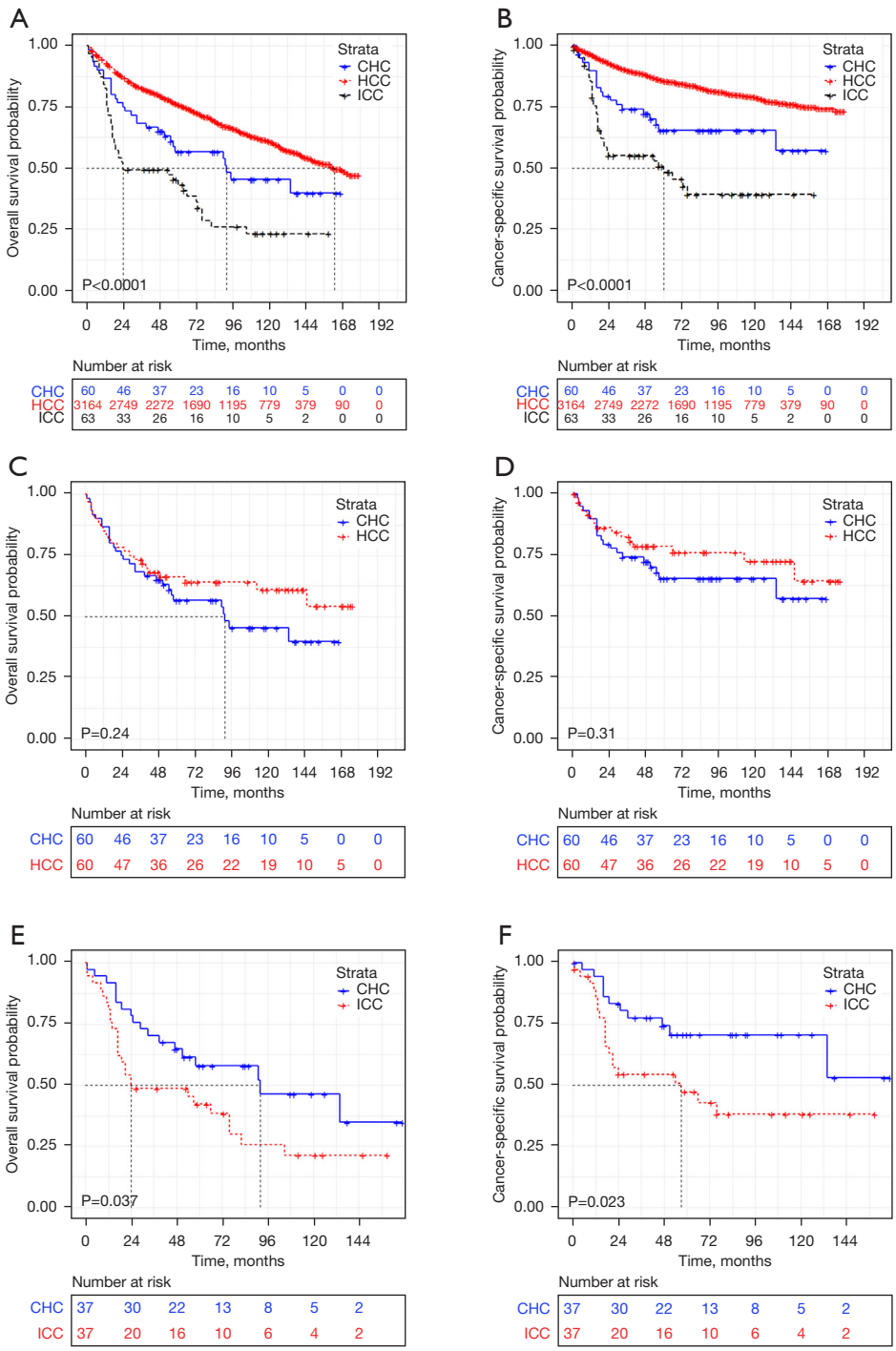

Figure 4 Kaplan-Meier survival analyses of overall survival and cancer-specific survival in LT recipients according to different subtypes of primary liver cancer. (A,B) CHC *vs.* HCC *vs.* ICC in all patients; (C,D) CHC *vs.* HCC in selected patients after PSM; (E,F) CHC *vs.* ICC in selected patients after PSM. LT, liver transplantation; CHC, combined hepatocellular-cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; PSM, propensity score matching.

Table 1 Risk scoring model for predicting post-transplantation outcomes of CHC patients

Factors	Overall survival			Cancer-specific survival		
	HR	β	Points	HR	β	Points
Multiple tumors	13.232	2.583	2	20.794	3.035	2
Tumor size >2 cm	7.836	2.059	1	9.352	2.236	1
Vascular invasion	3.640	1.292	1	5.036	1.617	1

CHC, combined hepatocellular-cholangiocarcinoma; HR, hazard ratio.

were stratified into 2 prognostic subgroups: the low-risk subgroup (total score ≤2 points) and the high-risk subgroup (total score >2 points or patients with extrahepatic metastasis, including lymph node metastasis and distant metastasis).

As indicated in *Figure 5A-5D*, the RSM showed good capacities to discriminate the high-risk subgroup from the low-risk subgroup (all P<0.05). In the training set, the C-index for OS and CSS was 0.721 (95% CI: 0.601–0.841) and 0.744 (95% CI: 0.595–0.893), respectively. The predictive performance of the model was also further validated in the validation cohort. The RSM displayed C-index values for OS and CSS separately as 0.710 (95% CI: 0.607–0.812) and 0.704 (95% CI: 0.573–0.835) (*Figure 6A-6F*, *Table 2*). Compared with the Milan and the University of California, San Francisco (UCSF) criteria, the RSM had higher C-index, 1-, 3- and 5-yr AUROC values in our study. Moreover, the AIC and BIC values of the RSM were lower than those of the 2 classical models, and ANOVA analyses showed significant differences between the RSM and other models (P<0.05, *Table 2*). Therefore, the RSM could be considered a novel and simple tool to evaluate the benefits of transplantation.

Discussion

Although several decades have passed since CHC was first reported in 1949, this cancer is still poorly understood due to its rarity and complexity, especially in treatment decision-making. For a single institute, it is a great challenge to obtain sufficient CHC cases for clinical research. On this basis, the SEER database showed unique advantages in large sample capacity and population-based research background. In this study, we utilized the SEER database to explore the role of LT and then developed an RSM to evaluate the benefits of transplantation in CHC patients.

The overall morbidity of CHC seemed to reveal an increasing trend with a borderline P value (P=0.060) between 2004 and 2015, suggesting that the prevention strategies for CHC still need to be taken seriously. Subgroup analyses by gender indicated that the morbidity remained stable in males and females, but there was an apparent male dominance, similar to that in HCC (35,36). In addition, the IBM for CHC did not decrease during the same period, and even had an upward trend among male patients. The steadiness of IBM may demonstrate that the treatment of CHC has not yet improved much in recent years. Therefore, more attention should be given to developing better therapeutic strategies to benefit CHC patients.

As the second most common (26.9%) surgical approach in our study, the role of LT is still a topic of debate. Theoretically speaking, LT provides curative resection opportunities and treats underlying liver disease, thereby decreasing tumor recurrence. However, among the 3 main subtypes of PLC, only HCC has been widely accepted as the leading indication of LT with a 5-yr OS of over 70% (5,17). According to the US latest national annual data report, the transplant rate for HCC candidates was still obviously higher than that for non-HCC candidates (94.3 *vs.* 58.3 per 100 waiting list-years) (37). As for ICC patients, some previous studies have reported disappointing survival (5-yr OS: 42–46%) and a high recurrence rate (43–53%) after transplantation, preventing them from being candidates for LT (38,39). In this context, CHC is also routinely regarded as a relative contraindication for LT due to its ICC component. Among CHC patients, the rate of LT gradually decreased from 33.3% in 2004 to 15.4% in 2015, with an APC of –8.9% (P=0.012).

Several previous retrospective studies have analyzed prognoses for CHC patients with LT, but some paradoxical conclusions have been drawn. Given the difficulty in preoperative diagnosis of CHC and the limited sample size of most studies (usually fewer than 30), it is not easy to

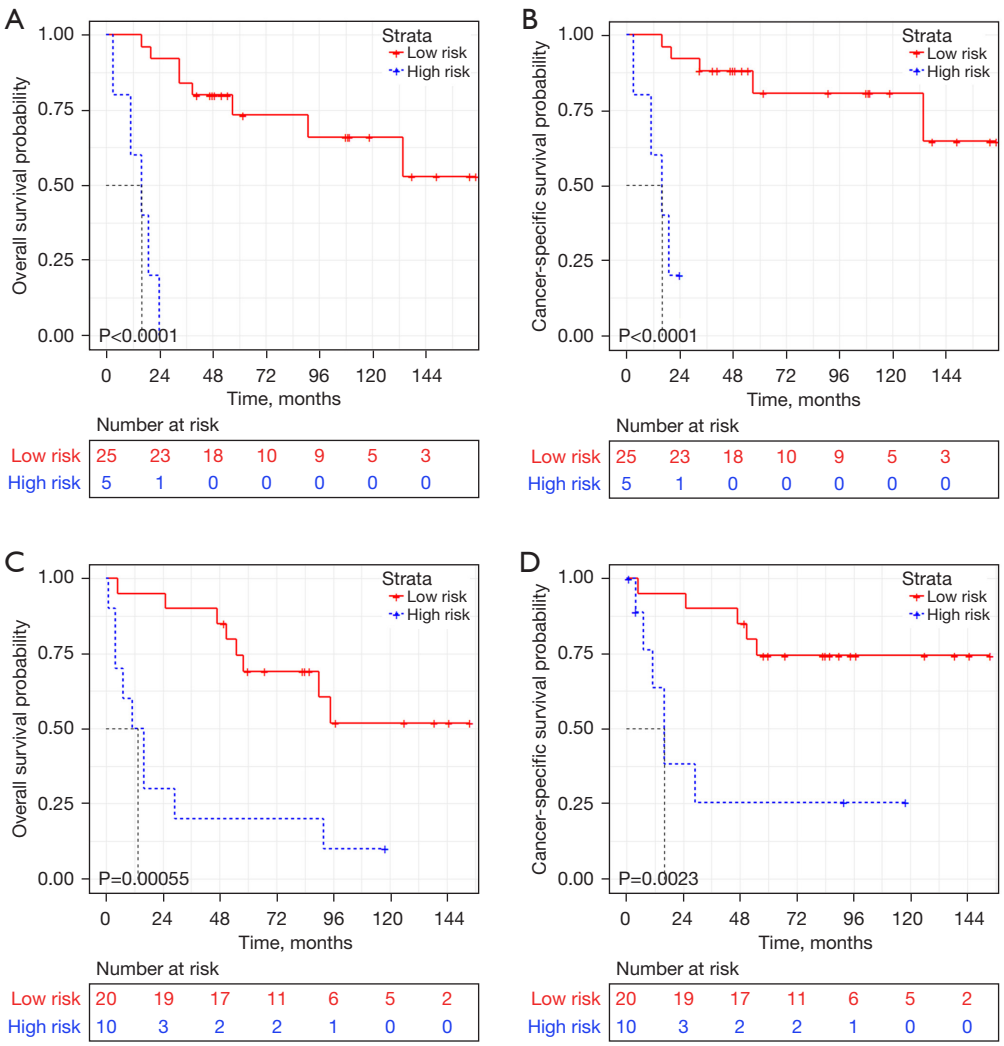

Figure 5 Kaplan-Meier survival analyses of overall survival and cancer-specific survival in LT recipients with CHC according to different prognostic subgroups categorized by the RSM. (A,B) Training set; (C,D) validation set. The low-risk group is defined as patients with scoring ≤2, and the high-risk group is defined as patients with scoring >2 or extrahepatic metastasis (including lymph node and distant metastasis). LT, liver transplantation; CHC, combined hepatocellular-cholangiocarcinoma; RSM, risk scoring model.

ultimately interpret these results (19,28-31,40-46). In our cohort, multivariate survival analyses confirmed surgery as an independent predictor for both OS and CSS (P<0.05). Meanwhile, the prognoses of LT recipients were superior to those of cases who underwent Hx and LD, regardless of tumor burden. This finding is similar to that obtained from a recent US multicenter study (28). In another French multicenter study, LT could benefit specific CHC patients with liver cirrhosis and a maximum tumor size of 5 cm (29). A transnational multicenter study also found that small tumors (≤3 cm), absence of lymph node metastasis, and short intensive care unit (ICU) stay were predictors for good post-transplantation prognoses (31). Some authors also observed encouraging results of LT in CHC patients and published their exploratory studies in the form of case reports or case series. Loosen *et al.* reported a 38-year-old male patient with advanced CHC who achieved an OS of 62 months after comprehensive treatment and LT (46). Ito *et al.* performed living donor LT in 4 CHC patients, 3 of whom within the Milan Criteria had recurrence-free survival of 65, 66, and 11 months, respectively (30). Maganty *et al.* observed that a CHC patient had tumor-

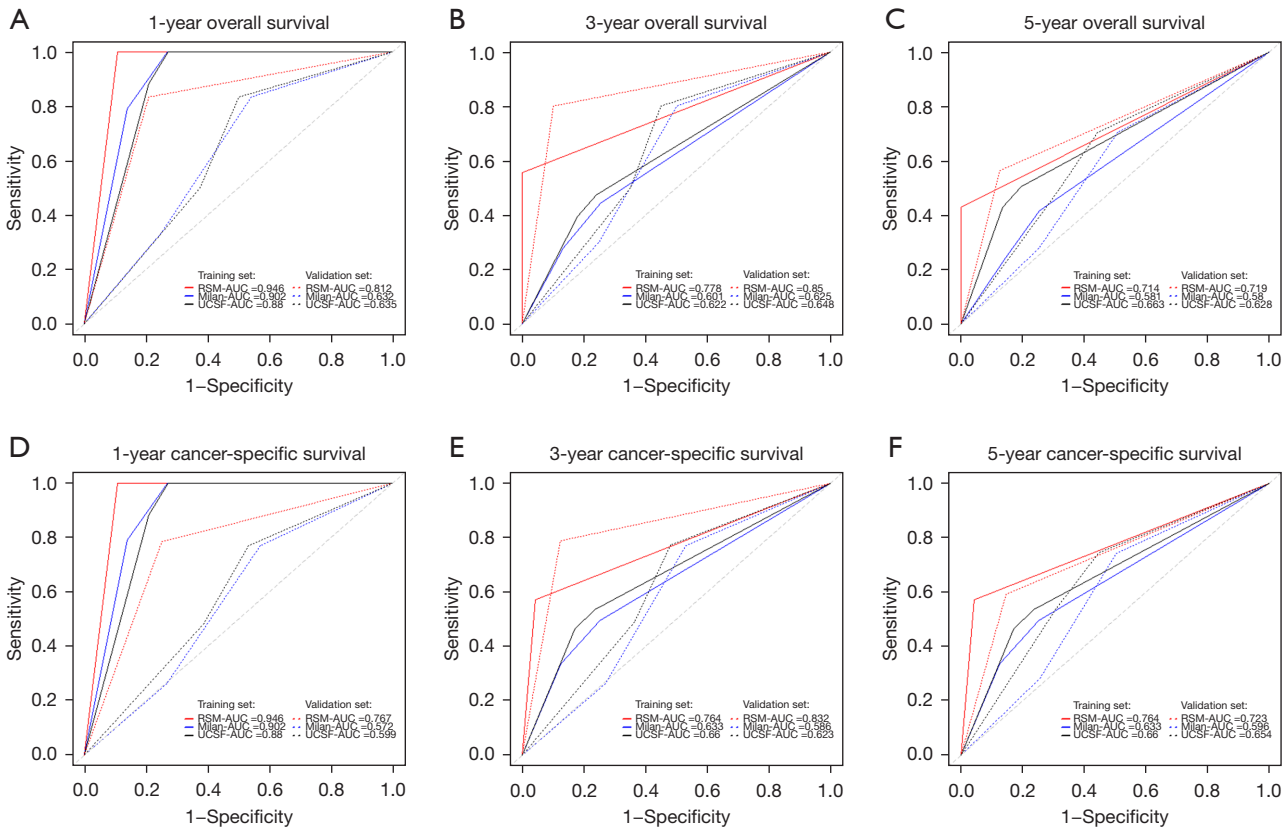

Figure 6 ROC analyses of the RSM, the Milan Criteria and the UCSF Criteria in predicting prognoses of patients at 1-, 3- and 5-year points of survival. (A-C) Overall survival; (D-F) cancer-specific survival. RSM, risk scoring model; AUC, area under the curve; UCSF, University of California, San Francisco; ROC, receiver operative characteristic.

free survival of over 8 years after LT (45). Notably, a recent meta-analysis conducted by Li *et al.* presented the opposite opinion. Although they were skeptical about LT, their results did not deny that LT was a non-inferior treatment option (18). Overall, the current evidence shows that a considerable number of CHC patients could benefit from LT compared to other therapies, and CHC should not be mechanically removed from the indications of LT.

Another major concern is the allocation of the donor liver. Due to the ethical requirements and the scarcity of livers available for transplantation, it is no surprise that potential prognoses for LT recipients with CHC must be comparable with those for patients with other well-accepted indications of LT. This study further examined the post-transplantation outcomes of patients with CHC, HCC, and ICC in the same period. Patients with HCC showed better survival than those with CHC and ICC after LT. Considering the relatively loose indications for transplantation of HCC, PSM was applied to reduce selection bias between groups. After matching, there was no survival difference between the CHC group and the HCC group (P>0.05). However, the CHC patients still had better transplantation outcomes than those who had ICC (P<0.05). The same results were also supported by Dageforde *et al.* (28), Lunsford *et al.* (40), and Gringeri *et al.* (47).

An RSM is an understandable and easy-to-use tool for stratifying patients at different risks to select suitable LT recipients. Through the multivariate Cox regression model, we incorporated 3 easily accessible clinicopathological factors and developed an RSM based on the β coefficient of each element (vascular invasion: 1 point; tumor size >2 cm: 1 point; multiple tumors: 2 points) to predict the prognoses of CHC patients undergoing LT. The LT recipients were then categorized into 2 prognostic subgroups: the low-risk group was defined as patients with total points ≤2, and the high-risk group was defined as total points >2 or patients with extrahepatic metastasis. The survival differences between the 2 groups were all significant, indicating that

Table 2 Analyses for prognostic performances among RSM, the Milan Criteria and the UCSF Criteria

Models	Overall survival							Cancer-specific survival						
	C-index (95% CI)	P	AIC	BIC	1-yr AUC	3-yr AUC	5-yr AUC	C-index (95% CI)	P	AIC	BIC	1-yr AUC	3-yr AUC	5-yr AUC
Training set (n=30)														
RSM	0.721 (0.601–0.841)	Ref	63.075	63.640	0.946	0.778	0.714	0.744 (0.595–0.893)	Ref	44.851	45.048	0.946	0.764	0.764
Milan	0.661 (0.528–0.795)	0.002†	75.002	76.132	0.902	0.601	0.581	0.690 (0.525–0.855)	0.013‡	53.058	53.452	0.902	0.633	0.633
UCSF	0.663 (0.520–0.806)	0.001††	75.327	76.457	0.880	0.622	0.663	0.690 (0.512–0.867)	0.008‡‡	53.914	54.308	0.880	0.660	0.660
Validation set (n=30)														
RSM	0.710 (0.607–0.812)	Ref	93.172	94.006	0.812	0.850	0.719	0.704 (0.573–0.835)	Ref	63.339	63.736	0.767	0.832	0.723
Milan	0.587 (0.461–0.713)	0.004§	103.531	105.197	0.632	0.625	0.580	0.625 (0.464–0.786)	0.022¶	70.564	71.360	0.572	0.586	0.596
UCSF	0.606 (0.484–0.728)	0.006§§	102.724	104.390	0.635	0.648	0.628	0.627 (0.471–0.783)	0.030¶¶	70.066	70.862	0.599	0.632	0.654

Chi-square: †, 9.927; ††, 10.252; ‡, 6.207; ‡‡, 7.063; §, 8.358; §§, 7.552; ¶, 5.226; ¶¶, 4.728. RSM, risk scoring model; UCSF, University of California, San Francisco; CI, confidence interval; AIC, Akaike information criterion; BIC, Bayesian information criterion; AUC, area under the curve; Ref, reference.

patients in the low-risk group were more suitable as LT candidates. In addition, the model achieved C-index values exceeding 0.700 for both OS and CSS in the training and validation sets. All these results showed that the RSM had a high prediction accuracy.

To date, there is no well-recognized LT selection criterion specifically for patients with CHC. Therefore, we compared the RSM with the 2 classical transplantation selection criteria, namely the Milan Criteria and the UCSF criteria, respectively. The Milan criteria were first proposed by Mazzaferro *et al.* in 1996, and specified that patients with a solitary tumor ≤5 cm or no more than 3 tumors and each tumor ≤3 cm could be put on the waiting list for LT (48). In 2001, a research team from UCSF raised expanded criteria that patients with a solitary tumor ≤6.5 cm or no more than 3 tumors with the largest lesion ≤4.5 cm and total tumor diameter ≤8 cm could also be considered transplantation candidates (49). In addition, both extrahepatic metastasis and vascular invasion were regarded as contraindications. Compared with the Milan and the UCSF Criteria, the RSM achieved higher C-index and AUROC values and lower AIC and BIC values, indicating that the RSM had a better discriminative capacity in CHC patients and did not need to be overfitted. Due to the ICC component, CHC patients are much more likely to have vascular invasion than those with HCC (32,50). A total of 10 (16.7%) CHC recipients exhibiting vascular invasion were classified into the low-risk group in our study cohort, with 5-yr OS of 70.0% and 5-yr CSS of 80.0%. Under such circumstances, completely denying LT in patients with vascular invasion may constitute a significant loss of potential opportunities to improve prognoses, which offered a possible explanation for inefficiencies of the Milan and the UCSF criteria in this study.

The role of LT in CHC has recently received increasing attention, but no prospective study has been published to date. In this high-volume retrospective study, utilizing the SEER database, we investigated the therapeutic value of LT and developed a novel RSM to evaluate the benefits of transplantation. Although our study has many merits, including but not limited to large sample capacity, definite pathological diagnosis, and complete 5-year follow-up, there were still some limitations. Firstly, the major drawback of this study is the inherent bias of the retrospective study design. Secondly, the SEER database lacks detailed clinicopathological data, which caused

unknown bias and limited further subgroup analysis. Lastly, the sample size after matching was not large enough due to the rarity of CHC, which may affect the reliability of our findings. In view of the positive results of the present study and the low morbidity of CHC, a multicenter prospective study is necessary to further confirm the role of LT in CHC patients.

Conclusions

Therapeutic strategies for CHC should be further improved, and some selected patients with CHC should also be considered potential candidates for LT. A novel and simple RSM has been developed to stratify LT recipients into 2 prognostic subgroups to assist in prognosis evaluation and clinical decision-making. The RSM outperformed the classical Milan and UCSF selection criteria in patients with CHC.

Acknowledgments

Funding: This study was supported by grants from the National Natural Science Foundation of China (Grant Nos. 31930020, 81870488, 81521004, and 81530048), Natural Science Foundation of Jiangsu Province (Grant No. BK20170142) and Key Laboratory of Liver Transplantation, Chinese Academy of Medical Sciences (Grant Nos. 2018PT31043 and 2019PT320015).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-5391/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5391/coif). XW serves as an Editor-in-Chief of *Annals of Translational Medicine* from August 2019 to July 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study followed the Declaration of Helsinki (as revised in 2013).

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(English Language Editors: J. Jones and J. Gray)

Cite this article as: Chen X, Sun S, Lu Y, Shi X, Wang Z, Chen X, Han G, Zhao J, Gao Y, Wang X. Promising role of liver transplantation in patients with combined hepatocellular-cholangiocarcinoma: a propensity score matching analysis. Ann Transl Med 2022;10(8):434. doi: 10.21037/atm-21-5391

