Original Article

Association of Pringle maneuver with postoperative recurrence and survival following hepatectomy for hepatocellular carcinoma: a multicenter propensity score and competing-risks regression analysis

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Background: The application of Pringle maneuver (PM) during hepatectomy reduces intraoperative blood loss and the need for perioperative transfusion, but its effect on long-term recurrence and survival for patients with hepatocellular carcinoma (HCC) remains controversial. We sought to determine the association between the application of PM and post-hepatectomy oncologic outcomes for patients with HCC.

Methods: Patients who underwent curative hepatectomy for HCC at 9 Chinese hospitals from January 2010 to December 2018 were identified. Using two propensity score methods [propensity score matching (PSM) and inverse probability of treatment weight (IPTW)], cumulative recurrence rate and cancer-specific mortality (CSM) were compared between the patients in the PM and non-PM groups. Multivariate competing-risks regression models were performed to adjust for the effect of non-cancer-specific mortality and other prognostic risk factors.

Results: Of the 2,798 included patients, 2,404 and 394 did and did not adopt PM (the PM and non-PM groups), respectively. The rates of intraoperative blood transfusion, postoperative 30-day mortality and morbidity were comparable between the two groups (all P>0.05). In the PSM cohort by the 1:3 ratio, compared to 382 patients in the non-PM group, 1,146 patients in the PM group also had the higher cumulative 5-year recurrence rate and CSM (63.9% and 39.1% *vs.* 55.3% and 31.6%, both P<0.05). Similar results were also yielded in the entire cohort and the IPTW cohort. Multivariate competing-risks regression analyses demonstrated that no application of the PM was independently associated with lower recurrence rate and CSM based on various analytical cohorts [hazard ratio (HR), 0.82 and 0.77 in the adjusted entire cohort, HR 0.80 and 0.73 in the PSM cohort, and HR 0.80 and 0.76 in the IPTW cohort, respectively].

Conclusions: The findings suggested that no application of PM during hepatectomy for patients with HCC reduced the risk of postoperative recurrence and cancer-specific death by approximately 20–25%.

Keywords: Hepatocellular carcinoma (HCC); Pringle maneuver (PM); recurrence; survival; hepatectomy

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most frequent cause of cancer-related mortality in the world (1). China alone accounts for more than one-half of the world's HCC patients (2). Hepatectomy provides a potentially curative opportunity for surgically eligible HCC patients (3). Because of recent progress in operative techniques and perioperative management, short- and long-term outcomes following hepatectomy for patients with HCC have improved with perioperative mortality being less than 3% and 5-year survival being up to 50% (4,5). Long-term survival remains, however, unsatisfactory because of the high incidence of cancer recurrence (the main cause of poor prognosis), which can range from 50–70% at 5 years after surgery (6). Identifying and reducing risk factors associated with postoperative recurrence and death is critical to improve long-term oncological outcomes for patients undergoing hepatectomy for HCC.

Apart from patient- and tumor-related factors, some surgery-related factors have been identified as potential risk factors associated with postoperative recurrence and death for patients with HCC, including width of resection margin, resection type (anatomical or non-anatomical), intraoperative blood loss and subsequent perioperative blood transfusion (7-11). Hepatic pedicle clamping [Pringle maneuver (PM)] has been a commonly used technique to reduce intraoperative blood loss and the need for blood transfusion (12). From the perspective of reducing intraoperative blood loss and the possibility of blood transfusion, PM may be beneficial to the long-term oncological prognosis of patients with HCC. PM can, however, lead to some degree of ischemia-reperfusion injury to the liver (13-15), which has been demonstrated to upregulate inflammatory factors and cytokines that correlate with cancer recurrence and tumor invasiveness (16-18). The relative advantages versus disadvantages of

Highlight box

Key findings

- In this large multicenter cohort study of 2,798 patients with hepatocellular carcinoma, the propensity score and competing-risks regression analysis revealed that no application of Pringle maneuver during hepatectomy was independently associated with lower cumulative recurrence rate and cancer-specific mortality.

What is known and what is new?

- The application of Pringle maneuver during hepatectomy reduces intraoperative blood loss and the need for perioperative transfusion, but it can lead to some degree of ischemia-reperfusion injury to the liver.
- Using two propensity score methods and competing-risk regression analysis, the effect of Pringle maneuver on long-term prognosis of hepatocellular carcinoma after hepatectomy was clarified.

What is the implication, and what should change now?

- On the premise of controllable intraoperative bleeding and ensuring operative safety, avoiding the application of Pringle maneuver during hepatectomy is a desirable manner to improve long-term oncologic survival for patients with hepatocellular carcinoma in the modern era.

PM related to decreased intraoperative blood loss/need for blood transfusions may be nullified or neutralized by the damage caused by hepatic ischemia-reperfusion. Therefore, the effect of PM on long-term oncologic prognosis for patients undergoing hepatectomy for HCC remains controversial. While some studies have reported that PM during hepatectomy for HCC was associated with a worse prognosis (19-21), others investigators did not note any adverse oncologic effect (22-24). Most previous studies were, however, from a single institution, had small sample sizes, and were subject to selection bias, which raises concerns about reliability and generalizability of the conclusions.

The objective of the current study was to characterize the effect of PM application on long-term recurrence and survival for patients with HCC using a prospectively-collected multicenter database. By using propensity score methods and competing-risks analysis to minimize selection bias and remove the effects of competitive events, the potential effects of PM application on long-term oncologic prognosis among patients undergoing hepatectomy for HCC were characterized. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-7/rc).

Methods

Patients

Using a large multicenter database (Mengchao Hepatobiliary Hospital, Eastern Hepatobiliary Surgery Hospital, Affiliated Hospital of Nantong University, Zhejiang Provincial People's Hospital, First Affiliated Hospital of Shandong First Medical University, First Affiliated Hospital of Anhui Medical University, Fourth Hospital of Harbin, Pu'er People's Hospital, and First Affiliated Hospital of Harbin Medical University), consecutive patients who underwent open hepatectomy with curative intent from January 2010 to December 2018 for HCC were identified. The data were prospectively collected using a standardized form. Curative hepatectomy (R0 hepatectomy) was defined as removal of all microscopic and macroscopic tumors with a microscopically negative margin. Patients who meet one of the following criteria were excluded: (I) less than 18 years old; (II) had received other anti-HCC treatment before hepatectomy; (III) recurrent HCC; (IV) underwent palliative hepatectomy [R1 (microscopically positive) or R2 (macroscopically positive) resection]; (V) were performed by other vascular occlusion methods instead of PM, including total vascular exclusion, hemi-hepatic vascular occlusion, and hepatic vascular exclusion with veno-venous bypass; (VI) other concomitant surgical procedures, including splenectomy, portosystemic shunt, biliary reconstruction, or gastrointestinal surgery during hepatectomy; (VII) with portal/hepatic vein tumor thrombus; (VII) loss to follow-up within 6 months after surgery; (IX) missing important prognostic variables. The study was censored on December 31, 2021. Data were analyzed from January 2022 to July 2022. The retrospective study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and the Ethical Guidelines for Clinical Studies of the Mengchao Hepatobiliary Hospital Ethics Committee (No. 2018-038-01), and was considered exempt from informed consent procedures.

Surgical procedures and application of PM

The indications for hepatectomy for HCC largely followed the Chinese Expert Consensus (25) and were generally consistent across participating hospitals. All operations were performed by surgeons with more than 5 years of extensive experience in hepatic surgery, and the resection criteria remained unchanged during the study to ensure consistency. The extent of hepatectomy (major or minor) was determined by tumor size and its deepest portion, combined with the minimum parenchymal sacrifice and the flattest cut surface. Major hepatectomy was defined as resection of three or more Couinaud liver segments, and minor hepatectomy was categorized as resection of fewer than three liver segments. Transection of the hepatic parenchyma was performed mainly using the clamp-crushing technique and/or ultrasound knife, and hemostasis was obtained with suture ligations and argon beam coagulator. The application of PM during hepatectomy depended on the habit and experience of the attending surgeon and the amount of intraoperative bleeding during the operation. The specific procedure of PM was performed by encircling the hepatoduodenal ligament with a catheter, and then the hepatic blood inflow was occluded by tightening the catheter. In most cases, the occlusion of PM was continuous if the transection time was less than 25–30 min; otherwise, intermittent PM occlusion was performed with cycles of 15–20 min clamping followed by 3–5 min of reperfusion, and the procedure was repeated until the end of liver parenchyma transection. Anatomical resection was

defined by the Brisbane 2000 system (26), whereas non-anatomical resections included wedge resection or limited resection. Anatomical resection was generally the first choice, while non-anatomical resection with a sufficient resection margin was often adopted to assure an adequate volume of the remaining liver.

Clinicopathological variables

Baseline characteristics of patients included age, gender, American Society of Anesthesiologists (ASA) score, hepatitis B virus (HBV), hepatitis C virus (HCV), cirrhosis, Child-Pugh grade, preoperative hemoglobin, and preoperative platelet counts. Tumor-related variables included preoperative alpha-fetoprotein (AFP) level, maximum tumor size, tumor number, satellite nodules, tumor encapsulation, tumor differentiation, and microvascular invasion. Operative variables included the extent of hepatectomy (major *vs.* minor), type of hepatectomy (anatomical *vs.* non-anatomical), resection margin, intraoperative blood loss, and intraoperative blood transfusion.

Follow-up

After hospital discharge, patients were prospectively followed at each participating hospital. Postoperative surveillance strategy for recurrence consisted of serum AFP level, ultrasonography, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI) of the chest and abdomen every 2 to 3 months for the first 2 years after surgery, and at least every 6 months thereafter. CT, MRI, angiography, bone scan, or positron emission tomography were performed when recurrence or distant metastasis was suspected. Treatment of tumor recurrence was based on the pattern of recurrent tumor, residual hepatic functional reserve, and general condition of the patient, and included re-resection, liver transplantation, local ablation therapy, transcatheter arterial chemoembolization, radiotherapy, systemic therapy, or supportive therapy. The dates of tumor recurrence, death, and last follow-up were recorded.

Study endpoints

The primary endpoint was long-term oncologic outcome, including cumulative recurrence rate and cancer-specific mortality (CSM), while the secondary endpoint were short-term outcomes including postoperative 30-day morbidity and mortality, respectively. Time to recurrence was calculated as the time from the date of surgery to the date of confirmation of HCC initial recurrence, while time to CSM was calculated from the date of hepatectomy to either the date of cancer-specific death (end event) or the date of non-cancer-specific death (competing-risk event) or the date of last follow-up (censored event). The main causes of non-CSM included hepatic deterioration or upper gastrointestinal hemorrhage as a result of severe liver cirrhosis and cardiovascular or cerebrovascular accidents. According to the Clavien-Dindo system (27), postoperative morbidities were classified into 5 grades and major morbidity was defined as Clavien-Dindo grade ≥3.

Statistical analysis

Clinicopathological characteristics were summarized using frequencies and percentages for categorical covariates and mean ± standard deviation (SD) or median [interquartile range (IQR)] for continuous covariates. Continuous variables were tested by the Student's *t*-test or Mann-Whitney U test, and categorical variables were analyzed using the chi-square test or Fisher exact test according to the situation. In addition to P values, standardized mean differences (SMD) were used to measure differences in baseline characteristics between the two comparative groups (the PM and non-PM groups), with SMD-values <0.1 to indicate negligible differences, and between 0.1 and 0.3 to indicate small differences.

After removing cases of postoperative early death (postoperative 90-day mortality), two propensity score methods [propensity score matching (PSM) and inverse probability of treatment weight (IPTW)] were used to balance baseline characteristics among patients in the PM and non-PM groups. Covariates entered into the propensity model included age, gender, ASA score, HBV, HCV, cirrhosis, Child-Pugh grade, preoperative hemoglobin, preoperative platelet counts, preoperative AFP level, maximum tumor size, tumor number, satellite nodules, tumor encapsulation, tumor differentiation, microvascular invasion, extent of hepatectomy, type of resection, intraoperative blood loss, intraoperative blood transfusion, and resection margin. The PSM method was performed as described by Rubin and Rosenbaum (28). To optimize the precision of the study, patients in the non-PM group were matched to individuals in the PM group in a 1:3 matching ratio by using a greedy, nearest neighbor matching algorithm. As for the IPTW procedure, a pseudo

population was created by weighting the inverse of the probability of a patient receiving the application of PM based on propensity score (29). The model preserved the size of the study population and no study participants were dropped (and statistical power lost), which was advantageous compared with the PSM method. Taking into account the effects of competing events (non-CSM) before the outcome events and other prognostic variables, the Fine-Gray sub-distribution hazard regression model was used to clarify the real impact of the application of PM on recurrence and CSM. On univariate analysis, variables with P<0.1 were entered into multivariate competing-risks regression models. Statistical analysis was performed using IBM SPSS (version22.0) and R (version 4.1.2) software. All statistical analyses were two-tailed, and P<0.05 was considered statistically significant.

Results

Study population

There were 3,796 patients who underwent open curative-intent hepatectomy for HCC during the study period for inclusion in the present study. After strict screening by inclusion and exclusion criteria, 2,798 patients were enrolled into this multicenter retrospective study. The flowchart of this study is shown in Figure S1. Among all patients, 2,365 (84.5%) were male and 433 (15.5%) were female; 2,261 patients (80.8%) had chronic HBV infection, and 278 patients (9.9%) were positive for HCV-RNA. The mean (SD) age of the entire cohort was 51.7 (10.8) years. There were 2,404 patients (85.9%, the PM group) and 394 patients (14.1%, the non-PM group) who did or did not have PM during hepatectomy, respectively.

Clinical characteristics and short-term outcomes

Comparisons of clinical characteristics and short-term outcomes among patients in the PM and non-PM groups in the entire cohort are shown in *Table 1*. Compared with individuals in the PM group, patients in the non-PM groups had a higher preoperative hemoglobin level (141.2±16.4 *vs.* 138.9±15.9 g/dL, P=0.013), platelet counts (164.6±68.0 *vs.* 157.4±57.8 $\times 10^9$/L, P=0.026), and intraoperative blood loss (median: 400 *vs.* 380 mL, P=0.036), yet a smaller tumor size (4.8±3.4 *vs.* 6.7±4.1 cm, P<0.001), a lower proportion of cirrhosis (45.7% *vs.* 56.2%, P<0.001), and a lower proportion of multiple tumors (15.7% *vs.* 21.0%, P=0.016), and a lower proportion of incomplete tumor encapsulation (79.7% *vs.* 84.7%, P=0.014). Notably, intraoperative blood transfusion (12.1% *vs.* 15.5%, P=0.058), postoperative 30-day mortality (2.0% *vs.* 1.0%, P=0.181), and postoperative 30-day morbidity (35.4% *vs.* 37.1%, P=0.514) were comparable between patients in the PM and non-PM groups.

Cases of postoperative early death within 90 days after surgery [83 (3.6%) in the PM group and 12 (3.1%) in the non-PM group] were excluded from analyses of long-term outcomes. After applying propensity score analysis, comparisons of clinical characteristics of the matched (the PSM cohort) and weighted (the IPTW cohort) study participants are shown in *Table 2*. There were no significant differences between the patients in the PM and non-PM groups for any covariate (all P>0.050 and SMD <0.200) (Figure S2).

Long-term oncologic outcomes

At a median (interquartile range) follow-up of 47.0 (20.1, 60.2) months, 1,576 (58.3%), 464 (17.2%) and 935 (34.6%) of 2,703 patients had recurrence, non-cancer-specific death, and cancer-specific death, respectively. Comparison of long-term oncologic outcomes between patients who adopted and did not adopt PM in the entire, PSM, and IPTW cohorts are shown in *Table 3*, respectively. In the entire cohort, cumulative 5-year recurrence and CSM of patients in the PM group were 66.3% and 43.5%, which were higher than individuals in the non-PM group, respectively (55.3% and 31.6%, P=0.001 and P<0.001, respectively). In the PSM cohort, compared with the 382 patients in the non-PM group, the 1,146 patients in the PM group had higher cumulative 5-year recurrence and CSM, respectively (63.9% and 39.1% *vs.* 55.3% and 31.6%, P=0.023 and P=0.009, respectively). Similar results were also noted in the IPTW cohort (65.8% and 39.5% *vs.* 57.6% and 35.0%, P=0.035 and P=0.043, respectively). Using a competing risk regression model, *Figure 1,2* depict the comparisons of cumulative recurrence and CSM between the patients in the PM and non-PM groups in the entire, PSM, and IPTW cohorts, respectively.

Univariate and multivariate analysis of recurrence and CSM

Univariate and multivariate competing-risks regression analyses were performed to identify risk factors associated with recurrence following hepatectomy for HCC in the

Table 1 Patients' clinical characteristics and short-term outcomes in the entire cohort

Variables	All (n=2,798)	PM (n=2,404)	Non-PM (n=394)	P value	SMD
Age, years	51.7±10.8	51.7±10.8	51.9±10.7	0.783	0.006
Male gender	2,365 (84.5)	2,041 (84.9)	324 (81.8)	0.117	0.061
ASA score >2	329 (11.7)	287 (11.9)	42 (10.7)	0.465	0.046
HBV (+)	2,261 (80.8)	1,939 (80.7)	322 (81.7)	0.618	0.035
HCV (+)	278 (9.9)	242 (10.1)	36 (9.4)	0.674	0.034
Cirrhosis	1,530 (54.7)	1,350 (56.2)	180 (45.7)	<0.001	0.221
Child-Pugh grade B	84 (3.0)	75 (3.1)	9 (2.3)	0.368	0.063
Preoperative hemoglobin, g/dL	140.9±16.3	138.9±15.9	141.2±16.4	0.013	0.130
Preoperative platelet counts, $\times 10^9$/L	158.5±59.4	157.4±57.8	164.6±68.0	0.026	0.121
Preoperative AFP >400 μg/L	940 (33.5)	824 (34.3)	116 (29.4)	0.058	0.096
Maximum tumor size, cm	6.2±3.8	6.7±4.1	4.8±3.4	<0.001	0.415
Multiple tumors	567 (20.3)	505 (21.0)	62 (15.7)	0.016	0.115
Satellite nodules	1,146 (40.9)	990 (41.2)	156 (39.6)	0.553	0.013
Incomplete tumor envelope	2,350 (83.9)	2,036 (84.7)	314 (79.7)	0.014	0.125
Poor tumor differentiation	2,283 (81.5)	1,969 (81.9)	314 (79.7)	0.294	0.046
Microvascular invasion	972 (34.7)	852 (35.4)	120 (30.5)	0.061	0.090
Major hepatectomy	653 (23.3)	555 (23.1)	98 (24.9)	0.438	0.051
Anatomical hepatectomy	667 (23.8)	584 (24.3)	83 (21.1)	0.164	0.084
Resection margin <1.0 cm	1,367 (48.8)	1,183 (49.2)	184 (46.7)	0.356	0.053
Intraoperative blood loss, mL	380 (300–480)	380 (300–450)	400 (300–550)	0.036	0.112
Intraoperative blood transfusion	351 (12.5)	290 (12.1)	61 (15.5)	0.058	0.098
Postoperative 30-day mortality	52 (1.9)	48 (2.0)	4 (1.0)	0.181	0.081
Postoperative 90-day mortality	95 (3.4)	83 (3.6)	12 (3.1)	0.679	0.027
Postoperative 30-day morbidity	996 (35.6)	850 (35.4)	146 (37.1)	0.514	0.039
Minor morbidity	681 (24.3)	575 (23.9)	106 (26.9)	0.201	0.071
Major morbidity	315 (11.3)	275 (11.4)	40 (10.2)	0.454	0.040

Values are n (%), mean ± standard deviation or median (interquartile range). ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; PM, Pringle maneuver; SMD, standardized mean difference.

entire cohort (Table S1), as well as in the PSM cohort (Table S2). As noted in *Table 4*, compared to the application of PM, the unadjusted and adjusted hazard ratios (HRs) of no application of PM on the risk of recurrence were 0.77 (95% CI: 0.66–0.91; P=0.001) and 0.82 (95% CI: 0.70–0.97; P=0.011) in the entire cohort, respectively, while its adjusted HR in the PSM cohort was 0.80 (95% CI: 0.67–0.95; P=0.012).

Univariate and multivariate competing-risks regression analyses were also performed to identify risk factors associated with CSM following hepatectomy for HCC in the entire cohort (Table S3), as well as in the PSM cohort (Table S4). Compared with the application of PM, the unadjusted and adjusted HRs of no application of PM on the risk of CSM were 0.68 (95% CI: 0.55–0.84; P<0.001) and 0.77 (95% CI: 0.61–0.96; P=0.031) in the entire cohort, respectively, while its adjusted HR in the PSM cohort was 0.73 (95% CI: 0.58–0.92; P=0.006) (*Table 4*).

Table 2 Patients' clinical characteristics in the PSM and IPTW cohorts

Variables	The PSM cohort*				The IPTW cohort*			
	PM (n=1,146)	Non-PM (n=382)	P value	SMD	PM (n=2,698)	Non-PM (n=2,880)	P value	SMD
Age, years	51.7±10.7	51.8±10.7	0.729	0.020	51.8±10.7	52.3±11.0	0.537	0.049
Male gender	959 (83.7)	321 (84.0)	0.936	0.009	2,320 (86.0)	2,479 (86.0)	0.989	0.001
ASA score >2	126 (11.0)	41 (10.7)	0.962	0.008	326 (12.1)	390 (13.6)	0.583	0.043
HBV (+)	963 (84.0)	318 (83.2)	0.779	0.021	2,215 (82.1)	2,352 (81.7)	0.876	0.008
HCV (+)	106 (9.2)	36 (9.4)	1.000	0.006	278 (10.3)	311 (10.8)	0.824	0.016
Cirrhosis	532 (46.4)	177 (46.3)	1.000	0.002	940 (34.8)	997 (34.6)	0.956	0.004
Child-Pugh grade B	27 (2.4)	8 (2.1)	0.921	0.018	80 (3.0)	108 (3.7)	0.589	0.043
Preoperative hemoglobin, g/dL	139.8±16.9	139.1±15.9	0.515	0.039	140.9±16.5	140.1±14.9	0.469	0.050
Preoperative platelet counts, $\times 10^9$/L	162.0±62.5	164.8±67.6	0.449	0.044	158.4±58.7	159.7±63.8	0.768	0.023
Preoperative AFP >400 μg/L	364 (31.8)	114 (29.8)	0.524	0.042	910 (33.7)	1,038 (36.0)	0.534	0.051
Maximum tumor, cm	5.2±3.9	4.8±3.4	0.533	0.020	5.5±3.9	5.1±3.6	0.154	0.097
Multiple tumors	205 (17.9)	62 (16.2)	0.508	0.044	544 (20.2)	637 (22.1)	0.520	0.047
Satellite nodules	465 (40.6)	155 (40.6)	1.000	<0.001	1,113 (41.3)	1,251 (43.4)	0.558	0.041
Incomplete tumor envelope	954 (83.2)	310 (81.2)	0.390	0.055	2,301 (85.3)	245,264 (85.6)	0.903	0.008
Poor tumor differentiation	948 (82.7)	310 (81.2)	0.536	0.041	2,230 (82.6)	2,378 (82.6)	0.975	0.002
Microvascular invasion	356 (31.1)	119 (31.2)	1.000	0.003	938 (34.8)	1,018 (35.4)	0.879	0.012
Major hepatectomy	260 (22.7)	95 (24.9)	0.421	0.051	618 (22.9)	620 (21.6)	0.609	0.040
Anatomical hepatectomy	277 (24.2)	82 (21.5)	0.312	0.064	662 (24.6)	878 (30.5)	0.106	0.138
Resection margin <1.0 cm	550 (48.0)	176 (46.0)	0.554	0.038	1,307 (48.5)	1,392 (48.3)	0.971	0.003
Intraoperative blood loss, mL	395 (300–480)	400 (300–550)	0.188	0.121	400 (300–500)	400 (300–550)	0.651	0.024
Intraoperative blood transfusion	158 (13.8)	61 (16.0)	0.332	0.061	310 (11.5)	308 (10.7)	0.673	0.039

Values are n (%), mean ± standard deviation or median (interquartile range). *, remove the cases of postoperative early death within 90 days after surgery (n=95). ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; IPTW, inverse probability of treatment weight; PM, Pringle maneuver; PSM, propensity score matching; SMD, standardized mean difference.

Decreased risk of recurrence and CSM due to no application of PM during hepatectomy were also noted in the IPTW cohort on both univariate and multivariate regression analyses (Tables S5,S6). In the IPTW cohort, the adjusted HRs of no application of PM on the risk of recurrence and CSM were 0.80 (95% CI: 0.66–0.97; P=0.029) and 0.76 (95% CI: 0.59–0.98; P=0.044), respectively (*Table 4*).

Discussion

Use of PM may improve short-term outcomes of hepatectomy by reducing intraoperative blood loss and the possibility of blood transfusion (30-32). The long-term oncologic outcomes associated with PM among patients with HCC remains more controversial. With the improvement of surgical technique and perioperative management (33,34). PM has become more of an optional intraoperative technique, being not as necessary during hepatectomy in many experienced hepatobiliary centers (35,36). However, in some cases during hepatectomy, PM is still routinely adopted as an effective means to keep the surgical field clean and improve surgical safety (37). In the present study, analyzing a prospectively-collected

Table 3 Long-term oncologic outcomes in the entire PSM and IPTW cohorts

Variables	The entire cohort			The PSM cohort			The IPTW cohort		
	PM (n=2,321)	Non-PM (n=382)	P value	PM (n=1,146)	Non-PM (n=382)	P value	PM (n=2,698)	Non-PM (n=2,880)	P value
Period of follow-up*, months	47 (20–60)	40 (17–60)	0.296	47 (24–60)	40 (17–60)	0.139	46 (21–60)	40 (16–60)	0.152
Recurrence during the follow-up	1,394 (60.1)	182 (47.6)	<0.001	674 (58.8)	182 (47.6)	<0.001	1,611 (59.7)	1,335 (46.3)	<0.001
Death during the follow-up	1,249 (53.8)	150 (39.3)	<0.001	596 (52.0)	150 (39.3)	<0.001	1,441 (53.4)	1,215 (42.2)	0.002
Cancer-specific death	843 (36.3)	92 (24.1)	<0.001	403 (35.2)	92 (24.1)	<0.001	971 (36.0)	717 (24.9)	0.001
Non-cancer-specific death	406 (17.5)	58 (15.2)	0.267	193 (16.8)	58 (15.2)	0.449	470 (17.4)	498 (17.2)	0.973
Time to recurrence**, months	34.0 (31.0–36.0)	47.0 (38.0–61.0)	0.001	36.0 (33.0–37.0)	47.0 (38.0–61.0)	0.023	35.0 (32.0–36.0)	47.0 (35.0–59.0)	0.035
1-year recurrence rate, %	31.7	26.6		28.8	26.6		32.4	28.9	
3-year recurrence rate, %	51.5	44.4		49.5	44.4		51.2	44.7	
5-year recurrence rate, %	66.3	55.3		63.9	55.3		65.8	57.6	
Time to CSM**, months	NA	NA	<0.001	NA	NA	0.009	72.0 (68.0–73.0)	NA	0.043
1-year CSM, %	9.6	8.0		7.9	8.0		9.7	7.8	
3-year CSM, %	28.0	17.4		25.3	17.4		27.0	18.6	
5-year CSM, %	43.5	31.6		39.1	31.6		39.5	35.0	

Values are n (%), median (interquartile range, *) or median (95% confidence interval, **) unless otherwise indicated. CSM, cancer-specific mortality; IPTW, inverse probability of treatment weight; NA, not attained; PSM, propensity score matching; PM, Pringle maneuver.

multicenter database with propensity score methods and competing-risks analysis (i.e., entire, PSM, and IPTW) demonstrated that the avoidance of PM was independently associated with decreased recurrence and CSM following hepatectomy for HCC (HR, 0.82 and 0.77 in the adjusted entire cohort; HR 0.80 and 0.73 in the PSM cohort; and HR 0.80 and 0.76 in the IPTW cohort). The data suggested that no application of PM reduced the risk of postoperative recurrence and cancer-specific death by approximately 20~25%. Avoiding hepatic pedicle clamping (i.e., PM) during hepatectomy is therefore desirable to improve long-term oncologic prognosis for patients with HCC.

The association of PM application with increased recurrence has been confirmed by several experimental studies. PM causes ischemia/reperfusion injury, resulting in complex metabolic, immunological and microvascular changes that contribute to hepatocellular damage and dysfunction (38-40). Hepatic ischemia/reperfusion injury affects the behavior of tumor cells by activating cell invasion and migration signaling pathways, stimulating tumor cell adhesion, and accelerating tumor recurrence (41,42). The underlying detrimental mechanism of PM relates to ischemia-reperfusion injury causing cellular damage by inducing free-radical formation, upregulating inflammatory cytokines, dysregulating mitochondrial calcium handling, and upregulating matrix metalloproteinases. These events promote intrahepatic micro-metastases and even distant metastases (43,44). Recent animal studies have also suggested that hypoxia *per se* may increase tumor activity and migration ability (45-47). Acute-phase inflammatory responses, microcirculatory barrier dysfunction, and hypoxia create an environment that may promote tumor progression, migration, and invasion. These processes may promote liver tumor growth and metastases, leading to postoperative tumor recurrence.

Given the crucial role of cirrhosis in the pathogenesis of HCC, minor hepatectomies and non-anatomical resections are often performed among patients with cirrhosis to preserve more liver parenchyma. In the entire cohort of this study, the majority of patients with HCC underwent minor hepatectomy and received PM. Theoretically, PM is more likely to be used in major hepatectomy. However,

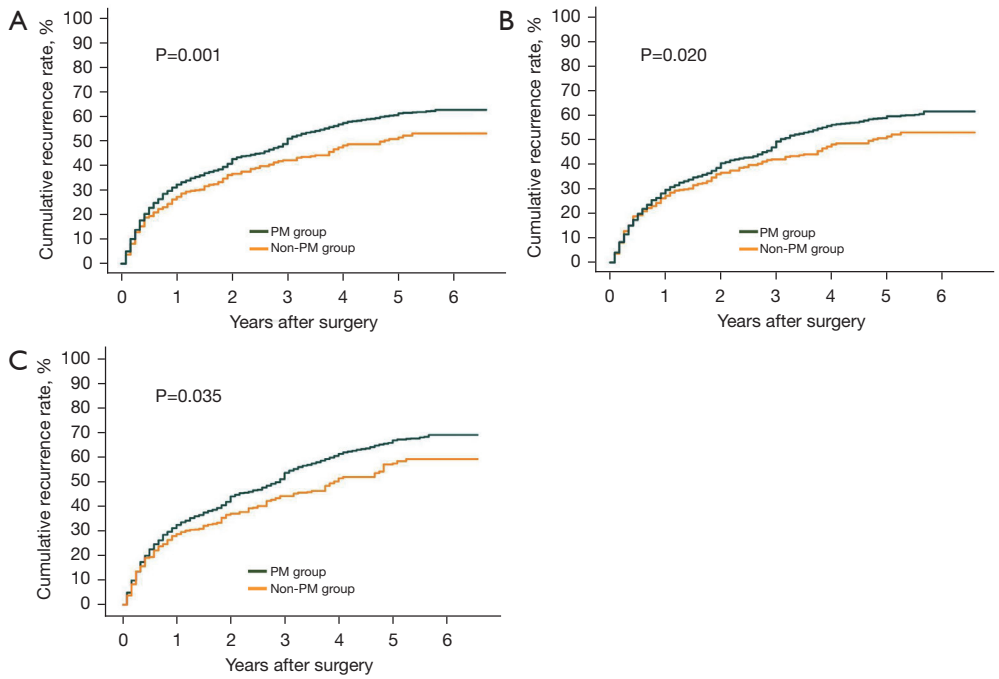

Figure 1 Cumulative recurrence rate curves between patients with and without the application of PM. (A) CRR in the entire cohort; (B) CRR in the PSM cohort; (C) CRR in the IPTW cohort. PM, Pringle maneuver; CRR, cumulative recurrence rate; PSM, propensity score matching; IPTW, inverse probability of treatment weight.

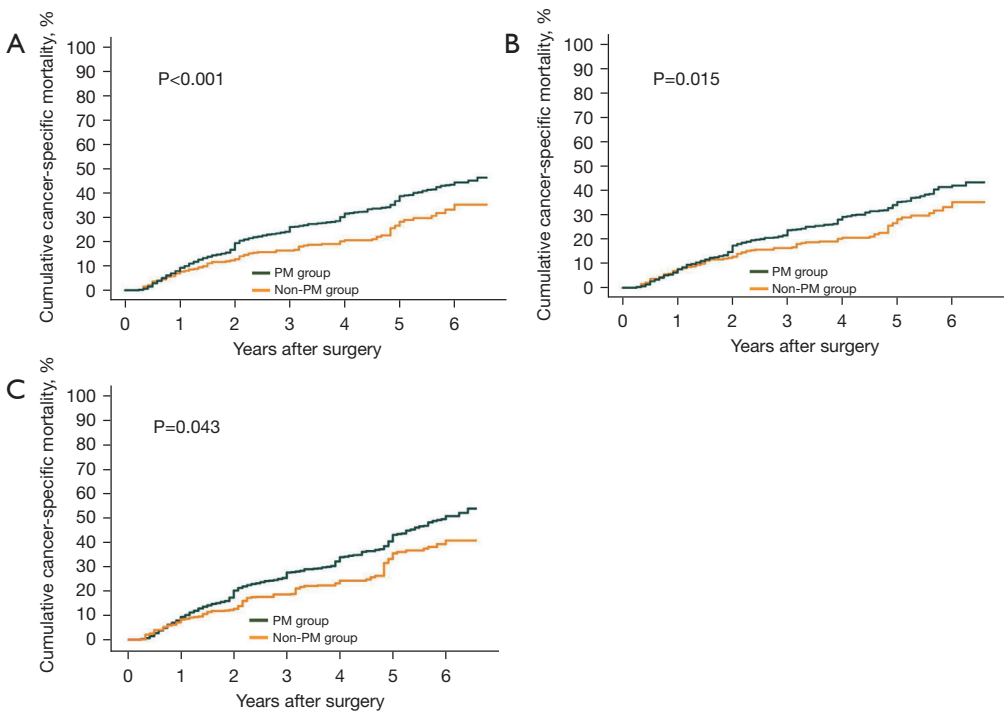

Figure 2 Cancer-specific mortality curves between patients with and without the application of PM. (A) CSM in the entire cohort; (B) CSM in the PSM cohort; (C) CSM in the IPTW cohort. PM, Pringle maneuver; CSM, cancer-specific mortality; PSM, propensity score matching; IPTW, inverse probability of treatment weight.

Table 4 Predicting the effect of the application of Pringle maneuver on recurrence and CSM in various analytical cohorts

Endpoints	Unadjusted (entire cohort)		Adjusted (entire cohort)[b]		Adjusted (PSM cohort)		Adjusted (IPTW cohort)	
	HR[a] (95% CI)	P	HR[a] (95% CI)	P	HR[a] (95% CI)	P	HR[a] (95% CI)	P
Recurrence	0.77 (0.66–0.91)	0.001	0.82 (0.70–0.97)	0.011	0.80 (0.67–0.95)	0.012	0.80 (0.66–0.97)	0.029
CSM	0.68 (0.55–0.84)	<0.001	0.77 (0.61–0.96)	0.031	0.73 (0.58–0.92)	0.006	0.76 (0.59–0.98)	0.044

[a], HRs are for the non-PM group, compared with the PM group. [b], adjusted for other prognostic variables such as age, gender, ASA score, HBV, HCV, cirrhosis, Child-Pugh grade, preoperative hemoglobin level, preoperative platelet counts, preoperative alpha-fetoprotein level, maximum tumor size, tumor number, satellite nodules, tumor encapsulation, tumor differentiation, microvascular invasion, extent of hepatectomy, type of hepatectomy, resection margin, intraoperative blood loss, and intraoperative blood transfusion. CI, confidence interval; CSM, cancer-specific mortality; HR, hazard ratio; IPTW, inverse probability of treatment weight; PSM, propensity score matching; PM, Pringle maneuver; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus.

some minor hepatectomies, such as posterosuperior segmentectomies (segment 7, segment 8, or segment 7-8) and complex core hepatectomies (segment 1 or segment 4-8), can be more complex and technically challenging, which makes the application of the PM more frequent in our real-world clinical practice.

In the present study, all surgeries were performed by surgeons with more than 5 years of extensive experience. However, we still observed variability in PM among different centers. This may be attributed to several factors. First, even experienced surgeons may have different levels of expertise and familiarity with PM due to differences in their training and practice settings. Second, the adoption and implementation of PM may vary across centers depending on factors such as local guidelines, institutional protocols, and resource availability. Additionally, the use of PM as a teaching tool for less experienced surgeons or trainees may contribute to the observed variability, as the performance of PM may be influenced by the learning curve and the need for close supervision. Lastly, certain centers may choose to adopt alternative techniques or approaches for managing HCC patients, leading to variations in the use of PM. It is important to consider these factors when interpreting the results of our study and evaluating the generalizability of our findings to different settings.

The strengths of the present study included the large sample size, the multicenter cohort, the prospectively collected database, the long-term follow-up, the convergence with real clinical situations, as well as study endpoints that more accurately reflect oncologic prognosis (recurrence and CSM, but not recurrence-free survival nor overall survival). In addition, analyses attempted to control for potential confounders by using the two propensity score methods (PSM and IPTW) and competing-risks regression analysis. Of note, non-cancer-specific death was more common among HCC patients, and the use of CSM as an outcome indicator was more consistent with oncological prognosis after adjusting for non-CSM as a competing factor. Propensity score analysis was carried out to balance the differences in baseline variables among patients with and without the application of PM during hepatectomy. After PSM or IPTW, the real impact of PM application on the oncologic prognosis of HCC after hepatectomy was more able to be determined. In addition, to further adjust for competing events and other confounding prognostic factors, a multivariate competing-risks regression analysis was applied to the entire and PSM cohorts (competing-risks analysis cannot be achieved in the IPTW cohort). A randomized controlled trial (RCT) to assess the impact of PM is not likely given the fundamental requirement of RCT not to allow arbitrary switching between intervention and control groups. As such, data from the current study were important because a rigorous statistical technique was adopted that accounted, as much as possible, for potent selection bias and confounding (37). While PM is effective to deal with intraoperative emergencies, such as increased blood oozing from the separated liver parenchyma particularly in cirrhotic patients, and sudden bleeding of intrahepatic large blood vessels, its use should be limited given the negative oncologic implications.

Several limitations of this study should be considered. This was a retrospective study. Although PSM, IPTW and competing-risks regression models were used, inherent limitations cannot be completely avoided. If an RCT study was to be conducted, how to ensure that switching between intervention and control groups would be challenging to address (i.e., that the adjusted rates are kept low, will be the key to obtaining rigorous and reliable conclusions). Patients from the current study also came exclusively from China. The main cause of HCC in East Asia (HBV infection) is

different from those in European and the United States (predominantly as HCV infection and alcoholic liver diseases) (48), so these variations may affect surgical outcomes. Therefore, the findings need to be externally validated, especially among Western patients. Another limitation was the difficulty to distinguish whether PM was used in a continuous or intermittent fashion due to the variability of PM techniques and the different habits of attending surgeons at different centers. However, previous studies have demonstrated that there was no difference in liver damage and prognosis between continuous and intermittent PM (49,50). Last but not least, in the present study, we only enrolled patients with HCC who underwent open hepatectomy. Due to the limited number during the study period and the potential influence of the initial learning curve of the laparoscopic procedures, patients who underwent laparoscopic resection were excluded from the analytic cohort. Further studies are needed to determine the possibility of our findings among patients undergoing laparoscopic hepatectomy for HCC.

Conclusions

In conclusion, this large multicenter study demonstrated that the lack of PM use during hepatectomy was associated with nearly 20–25% decreased risk of long-term recurrence and cancer-specific death for patients with HCC. Avoiding hepatic pedicle clamping (the application of PM) during hepatectomy if possible, should be considered more desirable as the data suggested this may lead to improved long-term oncologic outcomes among patients with HCC.

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Footnote

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Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-7/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-7/coif). T.M.P. serves as an unpaid Deputy Editor-in-Chief of *Hepatobiliary Surgery and Nutrition*. T.Y. serves as an unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. 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. The retrospective study was performed in accordance with the Declaration of Helsinki (as revised 2013) and the Ethical Guidelines for Clinical Studies of the Mengchao Hepatobiliary Hospital Ethics Committee (No. 2018-038-01), and was considered exempt from informed consent procedures.

References

1. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7:6.
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.

3. Gunasekaran G, Bekki Y, Lourdusamy V, et al. Surgical Treatments of Hepatobiliary Cancers. Hepatology 2021;73 Suppl 1:128-36.
4. Vibert E, Schwartz M, Olthoff KM. Advances in resection and transplantation for hepatocellular carcinoma. J Hepatol 2020;72:262-76.
5. Kamiyama T, Nakanishi K, Yokoo H, et al. Perioperative management of hepatic resection toward zero mortality and morbidity: analysis of 793 consecutive cases in a single institution. J Am Coll Surg 2010;211:443-9.
6. Zheng J, Kuk D, Gönen M, et al. Actual 10-Year Survivors After Resection of Hepatocellular Carcinoma. Ann Surg Oncol 2017;24:1358-66.
7. Katz SC, Shia J, Liau KH, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. Ann Surg 2009;249:617-23.
8. Sadamori H, Yagi T, Shinoura S, et al. Risk factors for major morbidity after liver resection for hepatocellular carcinoma. Br J Surg 2013;100:122-9.
9. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000;232:10-24.
10. Xu XF, Xing H, Han J, et al. Risk Factors, Patterns, and Outcomes of Late Recurrence After Liver Resection for Hepatocellular Carcinoma: A Multicenter Study From China. JAMA Surg 2019;154:209-17.
11. Kishi Y, Hasegawa K, Sugawara Y, et al. Hepatocellular carcinoma: current management and future development-improved outcomes with surgical resection. Int J Hepatol 2011;2011:728103.
12. Pringle JH. V. Notes on the Arrest of Hepatic Hemorrhage Due to Trauma. Ann Surg 1908;48:541-9.
13. Man K, Fan ST, Ng IO, et al. Tolerance of the liver to intermittent pringle maneuver in hepatectomy for liver tumors. Arch Surg 1999;134:533-9.
14. Teoh NC. Hepatic ischemia reperfusion injury: Contemporary perspectives on pathogenic mechanisms and basis for hepatoprotection-the good, bad and deadly. J Gastroenterol Hepatol 2011;26 Suppl 1:180-7.
15. Cho JY, Han HS, Choi Y, et al. Association of Remnant Liver Ischemia With Early Recurrence and Poor Survival After Liver Resection in Patients With Hepatocellular Carcinoma. JAMA Surg 2017;152:386-92.
16. Liu L, Ren ZG, Shen Y, et al. Influence of hepatic artery occlusion on tumor growth and metastatic potential in a human orthotopic hepatoma nude mouse model: relevance of epithelial-mesenchymal transition. Cancer Sci 2010;101:120-8.
17. Man K, Lo CM, Xiao JW, et al. The significance of acute phase small-for-size graft injury on tumor growth and invasiveness after liver transplantation. Ann Surg 2008;247:1049-57.
18. Orci LA, Lacotte S, Delaune V, et al. Effects of the gut-liver axis on ischaemia-mediated hepatocellular carcinoma recurrence in the mouse liver. J Hepatol 2018;68:978-85.
19. Hao S, Chen S, Yang X, et al. Adverse impact of intermittent portal clamping on long-term postoperative outcomes in hepatocellular carcinoma. Ann R Coll Surg Engl 2017;99:22-7.
20. Xiaobin F, Zipei L, Shuguo Z, et al. The Pringle manoeuvre should be avoided in hepatectomy for cancer patients due to its side effects on tumor recurrence and worse prognosis. Med Hypotheses 2009;72:398-401.
21. Wang CC, Iyer SG, Low JK, et al. Perioperative factors affecting long-term outcomes of 473 consecutive patients undergoing hepatectomy for hepatocellular carcinoma. Ann Surg Oncol 2009;16:1832-42.
22. Famularo S, Giani A, Di Sandro S, et al. Does the Pringle maneuver affect survival and recurrence following surgical resection for hepatocellular carcinoma? A western series of 441 patients. J Surg Oncol 2018;117:198-206.
23. Huang J, Tang W, Hernandez-Alejandro R, et al. Intermittent hepatic inflow occlusion during partial hepatectomy for hepatocellular carcinoma does not shorten overall survival or increase the likelihood of tumor recurrence. Medicine (Baltimore) 2014;93:e288.
24. Wei X, Zheng W, Yang Z, et al. Effect of the intermittent Pringle maneuver on liver damage after hepatectomy: a retrospective cohort study. World J Surg Oncol 2019;17:142.
25. Zhou J, Sun HC, Wang Z, et al. Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China (2017 Edition). Liver Cancer 2018;7:235-60.
26. Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg 2013;257:377-82.
27. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
28. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. Biometrics 1996;52:249-64.

29. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168:656-64.
30. Bogner A, Reissfelder C, Striebel F, et al. Intraoperative Increase of Portal Venous Pressure is an Immediate Predictor of Posthepatectomy Liver Failure After Major Hepatectomy: A Prospective Study. Ann Surg 2021;274:e10-7.
31. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236:397-406; discussion 406-7.
32. Torzilli G, Procopio F, Donadon M, et al. Safety of intermittent Pringle maneuver cumulative time exceeding 120 minutes in liver resection: a further step in favor of the "radical but conservative" policy. Ann Surg 2012;255:270-80.
33. Fritzmann J, Kirchberg J, Sturm D, et al. Randomized clinical trial of stapler hepatectomy versus LigaSure™ transection in elective hepatic resection. Br J Surg 2018;105:1119-27.
34. Bodzin AS, Leiby BE, Ramirez CG, et al. Liver resection using cavitron ultrasonic surgical aspirator (CUSA) versus harmonic scalpel: a retrospective cohort study. Int J Surg 2014;12:500-3.
35. Maurer CA, Walensi M, Käser SA, et al. Liver resections can be performed safely without Pringle maneuver: A prospective study. World J Hepatol 2016;8:1038-46.
36. Lee KF, Wong J, Ng W, et al. Feasibility of liver resection without the use of the routine Pringle manoeuver: an analysis of 248 consecutive cases. HPB (Oxford) 2009;11:332-8.
37. Piardi T, Lhuaire M, Memeo R, et al. Laparoscopic Pringle maneuver: how we do it. Hepatobiliary Surg Nutr 2016;5:345-9.
38. Man K, Ng KT, Lo CM, et al. Ischemia-reperfusion of small liver remnant promotes liver tumor growth and metastases--activation of cell invasion and migration pathways. Liver Transpl 2007;13:1669-77.
39. Ozaki M, Todo S. Surgical stress and tumor behavior: impact of ischemia-reperfusion and hepatic resection on tumor progression. Liver Transpl 2007;13:1623-6.
40. van der Bilt JD, Kranenburg O, Nijkamp MW, et al. Ischemia/reperfusion accelerates the outgrowth of hepatic micrometastases in a highly standardized murine model. Hepatology 2005;42:165-75.
41. van der Bilt JD, Kranenburg O, Borren A, et al. Ageing and hepatic steatosis exacerbate ischemia/reperfusion-accelerated outgrowth of colorectal micrometastases. Ann Surg Oncol 2008;15:1392-8.
42. Orci LA, Lacotte S, Oldani G, et al. The role of hepatic ischemia-reperfusion injury and liver parenchymal quality on cancer recurrence. Dig Dis Sci 2014;59:2058-68.
43. Lim C, Broqueres-You D, Brouland JP, et al. Hepatic ischemia-reperfusion increases circulating bone marrow-derived progenitor cells and tumor growth in a mouse model of colorectal liver metastases. J Surg Res 2013;184:888-97.
44. van Golen RF, Reiniers MJ, Olthof PB, et al. Sterile inflammation in hepatic ischemia/reperfusion injury: present concepts and potential therapeutics. J Gastroenterol Hepatol 2013;28:394-400.
45. van der Bilt JD, Soeters ME, Duyverman AM, et al. Perinecrotic hypoxia contributes to ischemia/reperfusion-accelerated outgrowth of colorectal micrometastases. Am J Pathol 2007;170:1379-88.
46. Yao B, Li Y, Niu Y, et al. Hypoxia-induced miR-3677-3p promotes the proliferation, migration and invasion of hepatocellular carcinoma cells by suppressing SIRT5. J Cell Mol Med 2020;24:8718-31.
47. Yao B, Li Y, Chen T, et al. Hypoxia-induced cofilin 1 promotes hepatocellular carcinoma progression by regulating the PLD1/AKT pathway. Clin Transl Med 2021;11:e366.
48. Lamarca A, Mendiola M, Barriuso J. Hepatocellular carcinoma: Exploring the impact of ethnicity on molecular biology. Crit Rev Oncol Hematol 2016;105:65-72.
49. Liu J, Wang W, Shi C, et al. The difference in prolonged continuous and intermittent Pringle maneuver during complex hepatectomy for hepatocellular carcinoma patients with chronic liver disease: A retrospective cohort study. Cancer Med 2021;10:8507-17.
50. Giuliante F, Ardito F, Pulitanò C, et al. Does hepatic pedicle clamping affect disease-free survival following liver resection for colorectal metastases. Ann Surg 2010;252:1020-6.

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Supplementary

Table S1 Univariate and multivariate competing-risks regression analysis of risk factors associated with recurrence in the entire cohort

Variables	HR comparison	UV HR (95% CI)	UV P value	MV HR (95% CI)	MV P value
Age	>60 *vs.* ≤60 years	0.93 (0.83–1.05)	0.270		
Gender	Male *vs.* Female	1.26 (1.09–1.47)	0.003	1.23 (1.05–1.44)	0.007
ASA score	>2 *vs.* ≤2	0.92 (0.79–1.07)	0.280		
HBV (+)	HBV *vs.* non-HBV	1.08 (0.95–1.23)	0.230		
HCV (+)	HCV *vs.* non-HCV	0.99 (0.85–1.17)	0.960		
Cirrhosis	Yes *vs.* No	1.21 (1.10–1.34)	<0.001	1.23 (1.11–1.37)	<0.001
Child-Pugh grade	B *vs.* A	1.06 (0.78–1.41)	0.720		
Preoperative hemoglobin	<110 *vs.* ≥110 g/dL	0.94 (0.71–1.24)	0.660		
Preoperative platelet counts	<100 *vs.* ≥100×10^9/L	0.93 (0.81–1.08)	0.360		
Preoperative AFP	>400 *vs.* ≤400 μg/L	1.19 (1.07–1.33)	0.001	1.05 (0.94–1.18)	0.280
Maximum tumor size	>5 *vs.* ≤5 cm	1.44 (1.31–1.59)	<0.001	1.23 (1.08–1.40)	<0.001
Tumor number	Multiple *vs.* Solitary	1.64 (1.46–1.85)	<0.001	1.37 (1.19–1.58)	<0.001
Satellite nodules	Yes *vs.* No	1.46 (1.32–1.61)	<0.001	1.15 (1.01–1.31)	<0.001
Tumor encapsulation	Incomplete *vs.* Complete	1.34 (1.17–1.54)	<0.001	1.21 (1.05–1.41)	<0.001
Tumor differentiation	Poor *vs.* Well or moderate	1.25 (1.11–1.42)	<0.001	1.04 (1.01–1.18)	<0.001
Microvascular invasion	Yes *vs.* No	1.39 (1.25–1.54)	<0.001	1.13 (1.01–1.27)	<0.001
Extent of hepatectomy	Major *vs.* Minor	1.46 (1.30–1.64)	<0.001	1.13 (0.97–1.31)	0.316
Type of hepatectomy	Non-anatomical *vs.* Anatomical	1.18 (1.05–1.32)	0.004	0.97 (0.85–1.11)	0.760
Resection margin	<1.0 *vs.* ≥1.0 cm	1.10 (0.99–1.21)	0.064	1.08 (0.98–1.20)	0.873
Intraoperative blood loss	>600 *vs.* ≤600 mL	1.26 (1.07–1.48)	0.005	1.06 (0.89–1.27)	0.230
Intraoperative blood transfusion	Yes *vs.* No	1.43 (1.22–1.67)	<0.001	1.11 (0.93–1.32)	0.107
Application of Pringle maneuver	No *vs.* Yes	0.77 (0.66–0.91)	0.001	0.82 (0.70–0.97)	0.011

ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MV, multivariate; UV, univariate.

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Table S2 Univariate and multivariate competing-risks regression analysis of risk factors associated with recurrence in the PSM cohort.

Variables	HR comparison	UV HR (95% CI)	UV P value	MV HR (95% CI)	MV P value
Age	>60 *vs.* ≤60 years	0.95 (0.82–1.12)	0.570		
Gender	Male *vs.* Female	1.27 (1.05–1.54)	0.016	1.25 (1.02–1.53)	0.026
ASA score	>2 *vs.* ≤2	0.97 (0.79–1.19)	0.770		
HBV (+)	HBV *vs.* non-HBV	1.14 (0.94–1.37)	0.170		
HCV (+)	HCV *vs.* non-HCV	0.94 (0.74–1.20)	0.650		
Cirrhosis	Yes *vs.* No	1.19 (1.04–1.36)	0.009	1.15 (1.00–1.33)	0.042
Child-Pugh grade	B *vs.* A	1.03 (0.64–1.66)	0.890		
Preoperative hemoglobin	<110 *vs.* ≥110 g/dL	1.09 (0.79–1.49)	0.600		
Preoperative platelet counts	<100 *vs.* ≥100×10^9/L	0.90 (0.75–1.08)	0.250		
Preoperative AFP	>400 *vs.* ≤400 μg/L	1.14 (0.98–1.32)	0.075	1.00 (0.86–1.17)	0.940
Maximum tumor size	>5 *vs.* ≤5 cm	1.45 (1.26–1.67)	<0.001	1.22 (1.00–1.50)	0.048
Tumor number	Multiple *vs.* Solitary	1.61 (1.37–1.91)	<0.001	1.37 (1.12–1.68)	0.001
Satellite nodules	Yes *vs.* No	1.37 (1.19–1.56)	<0.001	1.07 (0.90–1.27)	0.400
Tumor encapsulation	Incomplete *vs.* Complete	1.26 (1.06–1.51)	0.010	1.11 (0.92–1.34)	0.250
Tumor differentiation	Poor *vs.* Well or moderate	1.39 (1.17–1.66)	<0.001	1.20 (0.99–1.45)	0.058
Microvascular invasion	Yes *vs.* No	1.42 (1.23–1.65)	<0.001	1.20 (1.02–1.41)	0.029
Extent of hepatectomy	Major *vs.* Minor	1.47 (1.25–1.72)	<0.001	1.12 (0.88–1.43)	0.320
Type of hepatectomy	Non-anatomical *vs.* Anatomical	1.07 (0.92–1.25)	0.360		
Resection margin	<1.0 *vs.* ≥1.0 cm	1.22 (1.07–1.40)	0.003	1.23 (1.07–1.41)	0.003
Intraoperative blood loss	>600 *vs.* ≤600 mL	1.28 (1.04–1.56)	0.017	1.05 (0.85–1.31)	0.630
Intraoperative blood transfusion	Yes *vs.* No	1.38 (1.13–1.67)	0.001	1.06 (0.83–1.32)	0.640
Application of Pringle maneuver	No *vs.* Yes	0.81 (0.68–0.95)	0.012	0.80 (0.67–0.95)	0.012

ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MV, multivariate; PSM, propensity score matching; UV, univariate.

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Table S3 Univariate and multivariate competing-risks regression analysis of risk factors associated with cancer-specific mortality (CSM) in the entire cohort

Variables	HR comparison	UV HR (95% CI)	UV P value	MV HR (95% CI)	MV P value
Age	>60 *vs.* ≤60 years	0.89 (0.76–1.05)	0.170		
Gender	Male *vs.* Female	1.23 (1.02–1.50)	0.034	1.20 (0.97–1.46)	0.240
ASA score	>2 *vs.* ≤2	0.93 (0.76–1.13)	0.480		
HBV (+)	HBV *vs.* non-HBV	1.09 (0.92–1.29)	0.300		
HCV (+)	HCV *vs.* non-HCV	0.96 (0.78–1.19)	0.750		
Cirrhosis	Yes *vs.* No	1.30 (1.14–1.49)	<0.001	1.26 (1.09–1.44)	0.015
Child-Pugh grade	B *vs.* A	0.98 (0.66–1.46)	0.940		
Preoperative hemoglobin	<110 *vs.* ≥110 g/dL	1.09 (0.79–1.50)	0.570		
Preoperative platelet counts	<100 *vs.* ≥100×10^9/L	0.87 (0.73–1.05)	0.150		
Preoperative AFP	>400 *vs.* ≤400 μg/L	1.49 (1.31–1.70)	<0.001	1.18 (1.02–1.35)	0.001
Maximum tumor size	>5 *vs.* ≤5 cm	2.06 (1.81–2.34)	<0.001	1.50 (1.26–1.77)	<0.001
Tumor number	Multiple *vs.* Solitary	1.93 (1.68–2.23)	<0.001	1.39 (1.16–1.65)	<0.001
Satellite nodules	Yes *vs.* No	1.83 (1.61–2.08)	<0.001	1.33 (1.12–1.58)	<0.001
Tumor encapsulation	Incomplete *vs.* Complete	1.48 (1.22–1.79)	<0.001	1.15 (0.94–1.39)	0.090
Tumor differentiation	Poor *vs.* Well or moderate	1.84 (1.52–2.23)	<0.001	1.33 (1.08–1.62)	0.001
Microvascular invasion	Yes *vs.* No	1.75 (1.54–2.00)	<0.001	1.23 (1.06–1.42)	<0.001
Extent of hepatectomy	Major *vs.* Minor	1.97 (1.71–2.26)	<0.001	1.28 (1.07–1.52)	<0.001
Type of hepatectomy	Non-anatomical *vs.* Anatomical	1.54 (1.31–1.80)	<0.001	1.08 (0.90–1.29)	0.306
Resection margin	<1.0 *vs.* ≥1.0 cm	1.06 (0.93–1.20)	0.390		
Intraoperative blood loss	>600 *vs.* ≤600 mL	1.38 (1.14–1.68)	<0.001	1.06 (0.86–1.31)	0.939
Intraoperative blood transfusion	Yes *vs.* No	1.91 (1.60–2.27)	<0.001	1.32 (0.97–1.52)	0.091
Application of Pringle maneuver	No *vs.* Yes	0.68 (0.55–0.84)	<0.001	0.77 (0.61–0.96)	0.031

ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MV, multivariate; UV, univariate.

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Table S4 Univariate and multivariate competing-risks regression analysis of risk factors associated with cancer-specific mortality (CSM) in the PSM cohort

Variables	HR comparison	UV HR (95% CI)	UV P value	MV HR (95% CI)	MV P value
Age	>60 *vs.* ≤60 years	0.94 (0.75–1.16)	0.570		
Gender	Male *vs.* Female	1.22 (0.94–1.57)	0.120		
ASA score	>2 *vs.* ≤2	1.00 (0.76–1.32)	0.980		
HBV (+)	HBV *vs.* non-HBV	1.05 (0.82–1.34)	0.680		
HCV (+)	HCV *vs.* non-HCV	1.07 (0.80–1.42)	0.650		
Cirrhosis	Yes *vs.* No	1.35 (1.13–1.61)	<0.001	1.34 (1.11–1.62)	0.001
Child-Pugh grade	B *vs.* A	1.19 (0.68 – 2.07)	0.540		
Preoperative hemoglobin	<110 *vs.* ≥110 g/dL	1.25 (0.86–1.81)	0.230		
Preoperative platelet counts	<100 *vs.* ≥100×10^9/L	0.85 (0.69–1.06)	0.160		
Preoperative AFP	>400 *vs.* ≤400 μg/L	1.44 (1.20–1.73)	<0.001	1.10 (0.91–1.34)	0.300
Maximum tumor size	>5 *vs.* ≤5 cm	2.16 (1.81–2.57)	<0.001	1.52 (1.17 – 1.98)	0.001
Tumor number	Multiple *vs.* Solitary	1.83 (1.49–2.25)	<0.001	1.32 (1.03–1.70)	0.026
Satellite nodules	Yes *vs.* No	2.76 (1.48–2.10)	<0.001	1.29 (1.03–1.61)	0.023
Tumor encapsulation	Incomplete *vs.* Complete	1.47 (1.15–1.89)	0.002	1.11 (0.86–1.45)	0.400
Tumor differentiation	Poor *vs.* Well or moderate	2.19 (1.66–2.88)	<0.001	1.60 (1.19–2.14)	0.001
Microvascular invasion	Yes *vs.* No	1.88 (1.57–2.25)	<0.001	1.26 (1.02–1.55)	0.027
Extent of hepatectomy	Major *vs.* Minor	2.22 (1.84–2.68)	<0.001	1.41 (1.05–1.88)	0.019
Type of hepatectomy	Non-anatomical *vs.* Anatomical	1.23 (0.99–1.51)	0.051	0.92 (0.73–1.16)	0.520
Resection margin	<1.0 *vs.* ≥1.0 cm	1.20 (1.00–1.43)	0.046	1.20 (0.99–1.45)	0.051
Intraoperative blood loss	>600 *vs.* ≤600 mL	1.33 (1.04–1.70)	0.025	0.90 (0.68–1.19)	0.480
Intraoperative blood transfusion	Yes *vs.* No	1.90 (1.52–2.37)	<0.001	1.21 (0.92–1.59)	0.160
Application of Pringle maneuver	No *vs.* Yes	0.73 (0.58–0.92)	0.007	0.73 (0.58–0.92)	0.006

ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MV, multivariate; PSM, propensity score matching; UV, univariate.

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Table 5 Univariate and multivariate regression analysis of risk factors associated with recurrence in the IPTW cohort

Variables	HR comparison	UV HR (95% CI)	UV P value	MV HR (95% CI)	MV P value
Age	>60 *vs.* ≤60 years	0.91 (0.74–1.13)	0.417		
Gender	Male *vs.* Female	1.52 (1.12–2.07)	0.007	1.47 (1.10–1.95)	0.007
ASA score	>2 *vs.* ≤2	0.89 (0.70–1.12)	0.345		
HBV (+)	HBV *vs.* non-HBV	0.92 (0.74–1.15)	0.490		
HCV (+)	HCV *vs.* non-HCV	1.05 (0.79–1.38)	0.719		
Cirrhosis	Yes *vs.* No	1.25 (1.05–1.51)	0.013	1.26 (1.05–1.51)	0.011
Child-Pugh grade	B *vs.* A	0.92 (0.51–1.67)	0.794		
Preoperative hemoglobin	<110 *vs.* ≥110 g/dL	1.31 (0.87–1.97)	0.181		
Preoperative platelet counts	<100 *vs.* ≥100×10^9/L	0.95 (0.74–1.22)	0.725		
Preoperative AFP	>400 *vs.* ≤400 μg/L	1.30 (1.03–1.65)	0.025	1.13 (0.91–1.39)	0.243
Maximum tumor size	>5 *vs.* ≤5 cm	1.37 (1.13–1.66)	0.001	1.26 (1.01–1.52)	0.046
Tumor number	Multiple *vs.* Solitary	1.62 (1.26–2.08)	<0.001	1.21 (0.93–1.58)	0.138
Satellite nodules	Yes *vs.* No	1.70 (1.40–2.06)	<0.001	1.31 (1.06–1.62)	0.012
Tumor encapsulation	Incomplete *vs.* Complete	1.36 (1.07–1.73)	0.011	1.14 (0.90–1.45)	0.258
Tumor differentiation	Poor *vs.* Well or moderate	1.41 (1.10–1.82)	0.006	1.07 (0.84–1.37)	0.541
Microvascular invasion	Yes *vs.* No	1.80 (1.48–2.19)	<0.001	1.38 (1.11–1.71)	0.002
Extent of hepatectomy	Major *vs.* Minor	1.54 (1.26–1.89)	<0.001	1.14 (0.86–1.51)	0.319
Type of hepatectomy	Non-anatomical *vs.* Anatomical	1.25 (0.98–1.59)	0.068	1.03 (0.80–1.32)	0.829
Resection margin	<1.0 *vs.* ≥1.0 cm	1.27 (1.07–1.50)	0.004	0.98 (0.81–1.18)	0.849
Intraoperative blood loss	>600 *vs.* ≤600 mL	1.40 (1.01–1.94)	0.041	1.15 (0.89–1.50)	0.263
Intraoperative blood transfusion	Yes *vs.* No	1.32 (0.97–1.80)	0.074	1.01 (0.78–1.30)	0.916
Application of Pringle maneuver	No *vs.* Yes	0.80 (0.66–0.98)	0.035	0.80 (0.66–0.97)	0.029

ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IPTW, inverse probability of treatment weight; MV, multivariate; UV, univariate.

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Table S6 Univariate and multivariate regression analysis of risk factors associated with CSM in the IPTW cohort

Variables	HR comparison	UV HR (95% CI)	UV P value	MV HR (95% CI)	MV P value
Age	>60 *vs.* ≤60 years	0.95 (0.70–1.27)	0.738		
Gender	Male *vs.* Female	1.69 (1.15–2.47)	0.006	1.54 (1.07–2.20)	0.018
ASA score	>2 *vs.* ≤2	0.90 (0.63–1.25)	0.550		
HBV (+)	HBV *vs.* non-HBV	1.01 (0.73–1.40)	0.909		
HCV (+)	HCV *vs.* non-HCV	0.86 (0.58–1.27)	0.461		
Cirrhosis	Yes *vs.* No	1.42 (1.13–1.79)	0.003	1.56 (1.23–1.98)	<0.001
Child-Pugh grade	B *vs.* A	1.05 (0.59–1.86)	0.865		
Preoperative hemoglobin	<110 *vs.* ≥110 g/dL	1.01 (0.99–1.01)	0.732		
Preoperative platelet counts	<100 *vs.* ≥100×10^9/L	1.06 (0.76–1.49)	0.714		
Preoperative AFP	>400 *vs.* ≤400 μg/L	1.71 (1.32–2.22)	<0.001	1.27 (1.01–1.59)	0.044
Maximum tumor size	>5 *vs.* ≤5 cm	2.23 (1.76–2.81)	<0.001	1.98 (1.44–2.71)	<0.001
Tumor number	Multiple *vs.* Solitary	1.96 (1.45–2.62)	<0.001	1.13 (0.84–1.52)	0.404
Satellite nodules	Yes *vs.* No	2.43 (1.93–3.07)	<0.001	1.70 (1.32–2.19)	<0.001
Tumor encapsulation	Incomplete *vs.* Complete	1.51 (1.06–2.15)	0.021	1.02 (0.73–1.42)	0.872
Tumor differentiation	Poor *vs.* Well or moderate	2.19 (1.47–3.26)	<0.001	1.34 (0.91 – 1.98)	0.130
Microvascular invasion	Yes *vs.* No	2.62 (2.08–3.27)	<0.001	1.68 (1.31–2.15)	<0.001
Extent of hepatectomy	Major *vs.* Minor	2.21 (1.74–2.81)	<0.001	1.31 (0.96–1.79)	0.086
Type of hepatectomy	Non-anatomical *vs.* Anatomical	1.57 (1.12–2.21)	0.008	0.99 (0.70–1.39)	0.970
Resection margin	<1.0 *vs.* ≥1.0 cm	1.43 (1.15 – 1.77)	<0.001	0.89 (0.70–1.13)	0.367
Intraoperative blood loss	>600 *vs.* ≤600 mL	1.44 (1.06 – 1.97)	0.019	0.89 (0.65–1.22)	0.478
Intraoperative blood transfusion	Yes *vs.* No	1.74 (1.29–2.33)	<0.001	1.15 (0.88–1.51)	0.286
Application of Pringle maneuver	No *vs.* Yes	0.75 (0.57–0.99)	0.043	0.76 (0.59–0.98)	0.044

ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IPTW, inverse probability of treatment weight; MV, multivariate; UV, univariate.

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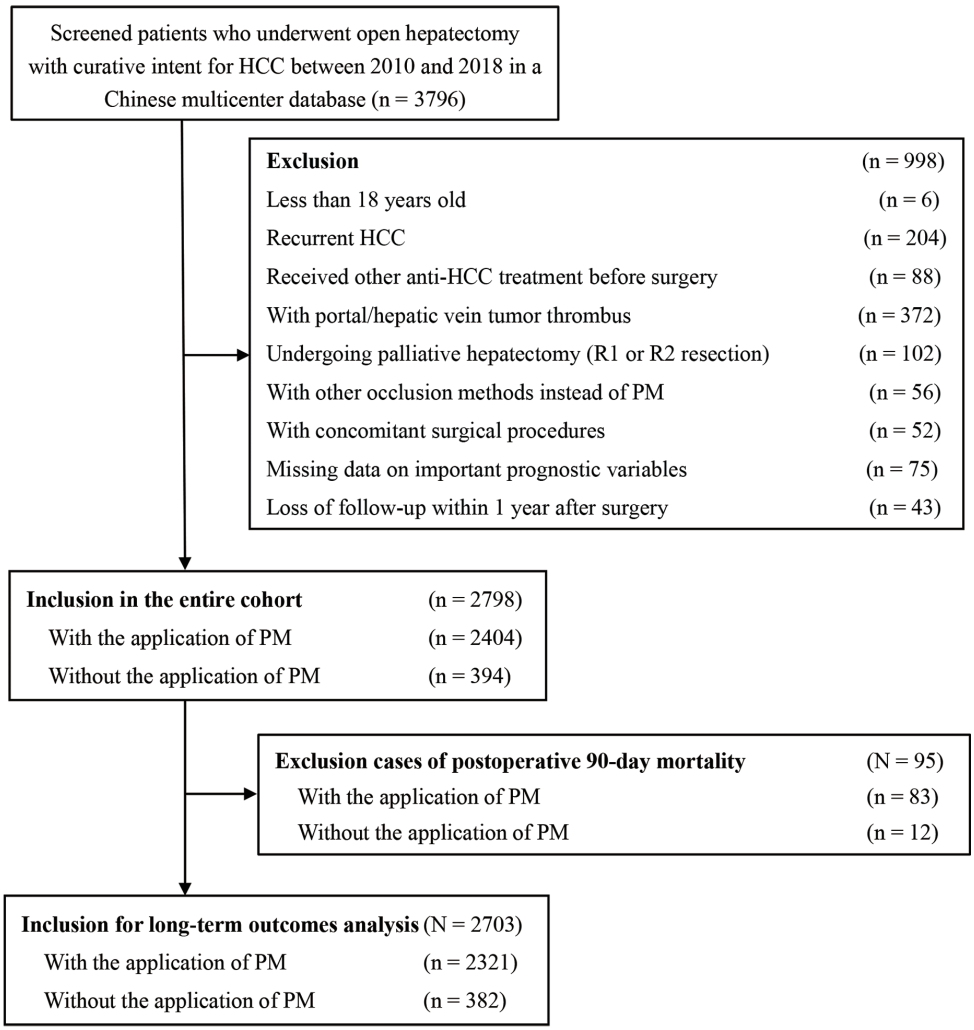

Figure S1 Study flowchart. HCC, hepatocellular carcinoma; PM, Pringle maneuver.

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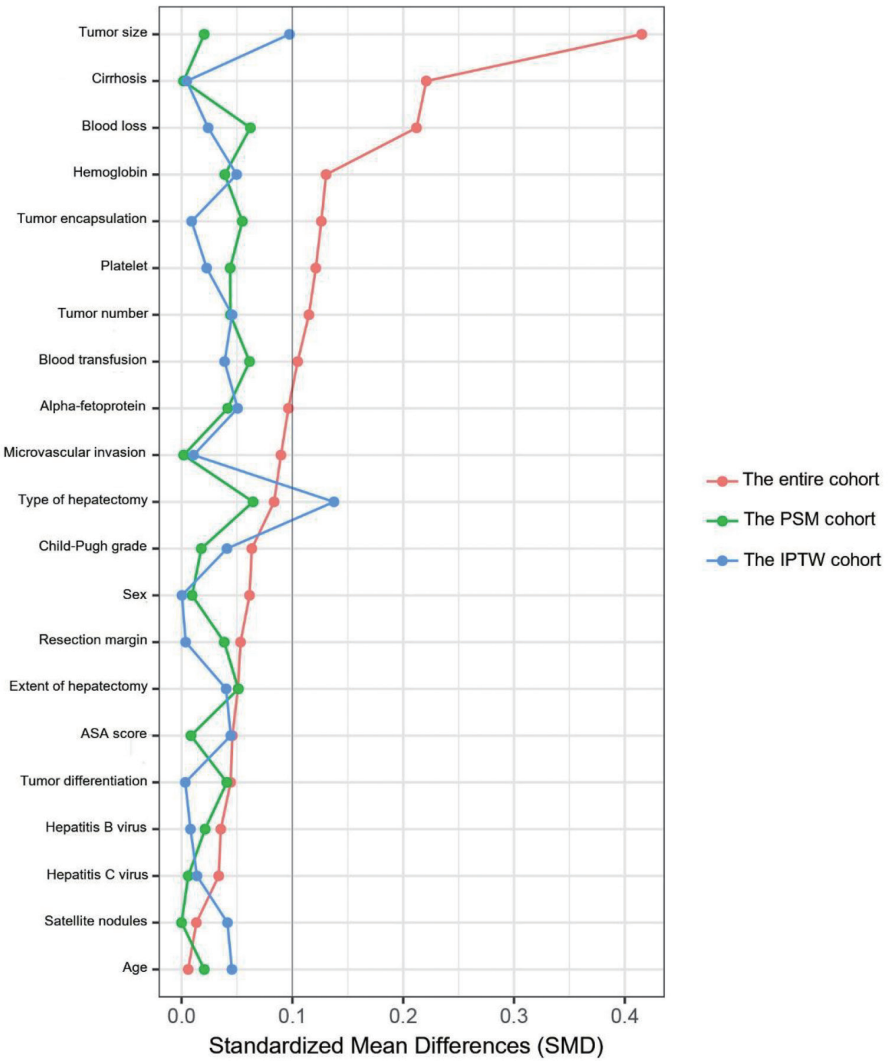

Figure S2 Comparisons of standardized mean difference of clinical variables between patients with and without the application of Pringle maneuver in the entire cohort (red dots), in the PSM cohort (green dots), and in the IPTW cohort (blue dots), respectively. ASA, American Society of Anesthesiologists; IPTW, inverse probability of treatment weight; PSM, propensity score matching.

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