Original Article

DOI: 10.5582/bst.2026.01126

Underrecognized cardiovascular complications after hepatectomy: population-level mortality burden from a multicentre population-attributable fraction (PAF) analysis

Junlong Dai[1,2,3,§], Zhancheng Qiu[1,§], Jimmy Che-To Lai[2,3,4,5], Yu Zhang[6], Fei Xie[7], Yu Yu[8], Kangyi Jiang[9], Tinghao Chen[10], Vincent Wai-Sun Wong[2,4,5], Tianfu Wen[1], Chuan Li[1,*]

[1] Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China;
[2] Medical Data Analytics Centre, The Chinese University of Hong Kong, Hong Kong SAR, China;
[3] Department of Medicine and Therapeutics, CUHK, Hong Kong SAR, China;
[4] State Key Laboratory of Digestive Disease, CUHK, Hong Kong SAR, China;
[5] Li Ka Shing Institute of Health Sciences, CUHK, Hong Kong SAR, China;
[6] Department of Hepatopancreatobiliary Surgery, Sichuan Academy of Medical Sciences (Sichuan Provincial People's Hospital), Chinese Academy of Sciences, Chengdu, Sichuan, China;
[7] Department of Hepatobiliary and Pancreatic Surgery, the First People's Hospital of Neijiang City, Neijiang, Sichuan, China;
[8] Department of Hepatopancreatobiliary Surgery, the Second People's Hospital of Yibin City, Yibin, Sichuan, China;
[9] Department of Hepatobiliary Surgery, People's Hospital of Leshan, Leshan, Sichuan, China;
[10] Department of General Surgery, Ziyang Central Hospital, Ziyang, Sichuan, China.

SUMMARY: Postoperative complications remain major determinants of outcomes after hepatectomy for hepatocellular carcinoma (HCC), but whether complications that prolong hospitalization are also those that contribute most to mortality remains unclear. This multicentre cohort study included 1,883 patients undergoing curative-intent hepatectomy for HCC across seven tertiary centers. Postoperative complications were categorized by organ system, and adjusted population-attributable fractions (PAFs) were calculated to estimate their contributions to 90-day mortality and prolonged hospital stay. Multivariable Cox models were used to assess associations with overall survival and recurrence-free survival. A divergence between hospitalization burden and mortality burden was observed. Liver surgery-specific complications accounted for the largest population-level burden of prolonged hospitalization (PAF 11.0%) and 90-day mortality (PAF 10.0%). Cardiovascular complications were the leading non-liver contributor to 90-day mortality (PAF 9.4%), despite a smaller contribution to prolonged hospitalization (PAF 4.1%). Pulmonary complications, cardiovascular complications, renal complications, and glucose dysregulation were independently associated with worse overall survival, whereas no complication domain was independently associated with recurrence-free survival. These findings show that postoperative recovery burden and mortality burden are not interchangeable after hepatectomy. Liver surgery-specific complications dominated hospitalization burden, whereas cardiovascular complications represented an underrecognized non-liver contributor to early mortality and worse long-term survival. An integrated perioperative framework incorporating systematic cardiovascular risk assessment may improve risk prioritization after hepatectomy for HCC.

Keywords: hepatocellular carcinoma, hepatectomy, postoperative complications, population-attributable fraction, overall survival

1. Introduction

Hepatectomy remains the cornerstone curative treatment for hepatocellular carcinoma (HCC) and offers the possibility of long-term survival (*1*). Despite advances in surgical techniques and increasing adoption of minimally invasive approaches, postoperative morbidity remains substantial, with complications continuing to compromise recovery, resource utilization, and long-term outcomes (*2*). Improving perioperative outcomes therefore remains a central objective in modern liver surgery.

Previous studies have described the incidence of postoperative complications and their associations with short- and long-term outcomes in patients undergoing hepatectomy for HCC (*2-4*). However, most analyses have focused on individual complication rates, relative risks, or conventional severity grading,

without accounting for their overall impact at the population level. For surgical outcome prioritization, neither complication incidence nor relative risk alone is sufficient. A rare complication with a high relative risk may be clinically serious but contribute less to the overall burden of adverse outcomes than a more common complication with a moderate relative risk. Conversely, a frequent complication may consume substantial postoperative resources even if its individual-level risk is modest.

In clinical practice of liver surgery, complications that prolong hospitalization or require direct surgical management, such as liver surgery-specific complications, may receive greater attention (*5-7*). By contrast, systemic complications, including cardiovascular events, may be less visible in routine surgical outcome assessment but may still contribute substantially to early postoperative mortality. The population-attributable fraction (PAF), widely used in epidemiological research, integrates exposure prevalence and relative risk to estimate the proportion of outcome burden associated with a given factor at the population level (*8*). Applied to postoperative complications, PAF may help distinguish complications that primarily increase healthcare burden, such as prolonged length of stay, from those that contribute disproportionately to mortality. This distinction is particularly relevant after hepatectomy, where postoperative risk reflects both liver-specific injury and systemic perioperative vulnerability (*9*).

In this multicentre cohort study, we systematically categorized postoperative complications following hepatectomy for HCC by organ system and applied PAF-based analyses to quantify their relative contributions to short- and long-term outcomes. Through this approach, we aimed to refine risk stratification and provide a population-level framework to prioritize perioperative interventions.

2. Materials and Methods

2.1. Study design and data source

This multicentre retrospective cohort study included consecutive adult patients undergoing curative-intent hepatectomy for HCC at seven high-volume tertiary hepatobiliary centers in China between January 2014 and December 2019.

Curative intent was defined as complete macroscopic tumor removal without radiologic or intraoperative evidence of distant metastasis. Only patients who achieved R0 resection, confirmed by histopathological examination demonstrating microscopically negative margins, were eligible for inclusion. Patients undergoing palliative or non-curative procedures were excluded.

Clinical data were extracted from institutional electronic medical record systems using predefined case report forms. Collected variables included demographic characteristics, comorbidities, preoperative laboratory parameters, tumor burden and pathological features, operative details, and postoperative outcomes. Postoperative complications were identified through systematic review of inpatient medical and nursing records and were adjudicated according to uniform predefined criteria across centers to ensure inter-institutional consistency.

2.2. Participants

The date of hepatic resection was defined as the index date. Inclusion criteria were age ≥ 18 years, first liver resection, histologically confirmed HCC, R0 resection, and availability of complete medical and nursing records for postoperative complication assessment. Exclusion criteria included non-curative or palliative procedures, concomitant major resection of other organs, insufficient data for complication adjudication, unreliable follow-up, and Barcelona Clinic Liver Cancer (BCLC) stage C disease.

Only patients with HCC were included to ensure population homogeneity, as intrahepatic cholangiocarcinoma and combined tumors differ substantially in tumor biology, prognostic determinants, and postoperative management, particularly regarding the use of adjuvant chemotherapy (*e.g.*, ABC-02 regimen), which may confound long-term outcomes.

A total of 2,457 patients were screened. After applying predefined inclusion and exclusion criteria, 1,883 patients were included in the final analysis (Figure 1). Patients were followed from the index date until death, tumor recurrence, loss to follow-up, or the administrative censoring date of 30 June 2023, whichever occurred first.

The study was conducted in accordance with the Declaration of Helsinki (2013) and was approved by the Biomedical Ethics Committee of West China Hospital (approval number: 2026-758), with informed consent waived owing to the retrospective nature of the study.

2.3. HCC diagnosis and management

HCC diagnosis and management followed contemporary national guidelines (*1*). Diagnosis was established by characteristic radiologic findings on multiphasic contrast-enhanced CT or MRI or confirmed histologically when necessary. All patients underwent standardized preoperative evaluation, including assessment of liver function reserve (Child–Pugh class and MELD score), viral hepatitis status, and tumor burden using contrast-enhanced imaging. Surgical candidacy was determined through multidisciplinary discussion, taking into account liver reserve, tumor stage, and overall fitness for major hepatectomy. Perioperative management followed institutional

standardized protocols, including intraoperative blood loss control strategies and structured postoperative monitoring. Antiviral therapy was administered to patients with active hepatitis B virus infection according to guidelines. Postoperative surveillance consisted of clinical evaluation, serum AFP testing, and imaging every 3–6 months during the first 2 years and every 6 months thereafter. Recurrence was defined radiologically or histologically.

2.4. Outcome and post-surgery complications definitions

The primary outcome was 90-day all-cause mortality. Secondary outcomes included prolonged length of hospital stay, overall survival, and recurrence-free survival. Prolonged length of hospital stay was defined as hospitalization duration above the 75th percentile of the cohort distribution. Overall survival and recurrence-free survival were calculated from the date of surgery to death and tumor recurrence, respectively.

Postoperative complications were defined and categorized according to standardized criteria summarized in Supplementary Table S1 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*). Complication events were assessed during the index hospitalization and were independently reviewed by two investigators. Any discrepancies were resolved through discussion and consensus. Complications were classified using the Clavien–Dindo classification (*10*). Severe complications were defined as grade ≥ III. In addition, the Comprehensive Complication Index (CCI) was calculated to quantify the cumulative burden of postoperative morbidity (*11*).

Liver surgery-specific complications were defined in accordance with the framework proposed by the International Study Group of Liver Surgery (ISGLS), including post-hepatectomy liver failure (PHLF), bile leakage, postoperative ascites, postoperative blood transfusion, and reoperation. PHLF and bile leakage were defined according to ISGLS consensus criteria (Supplementary Figure S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*) (*12,13*).

Other postoperative complications were categorized into cardiovascular, pulmonary, renal, infection-related, metabolic and electrolyte, and gastrointestinal complications based on predefined clinical criteria. Cardiovascular complications were restricted to primary cardiovascular events, including new-onset or clinically significant arrhythmia and acute cardiac events. Instead, postoperative hemodynamic instability was recorded separately as an indicator of postoperative severity. Composite complication groups were constructed to reflect organ-system morbidity, while individual components were also analyzed where appropriate.

2.5. Statistical analysis

2.5.1. Descriptive statistics

Continuous variables were summarized as mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables were presented as counts and percentages. Between-group comparisons were performed using Student's *t*-test or Wilcoxon rank-sum test for continuous variables and chi-square or Fisher's exact test for categorical variables, as appropriate. Statistical significance was defined as a two-sided p-value < 0.05. All analyses were conducted using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

2.5.2. Missing data and multiple imputations

Missing data patterns were evaluated prior to analysis (Supplementary Figure S2, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*). Variables with missing values were imputed using multiple imputations by chained equations under the missing-at-random assumption. Five imputed datasets were generated with 20 iterations per dataset (*14*). Imputation diagnostics demonstrated good agreement between observed and imputed values (Supplementary Figure S3 and S4, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*). Exposure variables, outcomes, and derived composite indices were not imputed. Estimates from imputed datasets were combined using Rubin's rules.

2.5.3. Risk estimation for short-term outcomes

For binary outcomes (90-day mortality and prolonged length of stay), adjusted relative risks (RRs) with 95% confidence intervals (CIs) were estimated using Poisson regression models with log link and robust variance estimators. Each organ system–specific complication group was modeled independently as the exposure variable to minimize collinearity between complication domains and adjusted for predefined demographic characteristics, comorbidities, liver function parameters, tumor stage, and surgical factors. Restricted cubic spline functions were applied to assess potential non-linear associations between selected continuous covariates and binary outcomes (Supplementary Table S2, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*).

Pairwise correlations among complication domains were assessed using Phi coefficients to evaluate clustering and potential collinearity (Supplementary Figure S5, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*). The number of complication domains per patient was also calculated to describe the extent of co-occurrence. Although co-occurrence of postoperative complications was clinically relevant, most patients had no complication

domain or only a single complication domain, indicating that extensive overlap across domains was not the predominant pattern. Because postoperative complications may still co-occur or arise sequentially within shared clinical cascades, simultaneous inclusion of multiple complication domains in the same model could yield unstable estimates and obscure the total burden associated with each domain. Therefore, each complication domain was modeled separately. These models were intended to estimate total population-level association and attributable burden of each domain, rather than to partition mutually exclusive causal effects among competing complications.

2.5.4. Population-attributable fraction

To quantify the population-level impact of each complication, adjusted PAFs were calculated using a counterfactual approach. PAF was calculated using the formula below:

$$PAF = \frac{Risk_{observed} - Risk_{counter\ factual}}{Risk_{observed}}$$

For each complication, predicted outcome risks were estimated under observed exposure and under a hypothetical scenario in which the complication was absent. Bootstrap resampling (200 replications within each imputed dataset) was performed to derive 95% confidence intervals and P values (*8*).

2.5.5. Survival analysis for long-term outcomes

OS and recurrence-free survival RFS were estimated using the Kaplan–Meier method and compared using the log-rank test. Patients with unavailable long-term followup (n = 2, 0.1%) and recurrence status (n = 73, 3.9%) were excluded from recurrence-free survival analyses. Multivariable Cox proportional hazards models were constructed to estimate adjusted hazard ratios (HRs) with 95% CIs. Each complication was entered separately as an exposure variable and adjusted for predefined demographic characteristics, liver function parameters, tumor burden, and surgical factors. Cox models were fitted within each imputed dataset and pooled using Rubin's rules. The proportional hazards assumption was evaluated using Schoenfeld residuals.

2.5.6. Sensitivity analyses

Three predefined sensitivity strategies were implemented to evaluate the robustness of the findings. First, alternative multivariable adjustment strategies were applied to assess stability of RR and PAF estimates (Supplementary Table S3, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*). Model A served as the primary model; Model B (tumor-burden–focused) was additionally adjusted for pathological aggressiveness; Model C (comorbidity-focused) was additionally adjusted for comorbidities; and Model D (surgery-focused) emphasized surgery details and prior abdominal surgery. Covariate selection in each model was constrained according to the events-per-variable (EPV) principle, maintaining EPV ≥ 10. Second, analyses were repeated after excluding patients with BCLC stage B disease. Third, PAF estimates were recalculated under alternative adjustment strategies to evaluate the robustness of the counterfactual approach (Supplementary Figure S6, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*).

3. Results

3.1. Study population and baseline characteristics

A total of 1,883 patients undergoing curative-intent hepatectomy for HCC were included in the analysis (Figure 1). The cohort was predominantly male (84.6%), with a mean age of 53.5 ± 11.6 years and a mean BMI of 23.2 ± 3.2 kg/m². Hypertension and diabetes mellitus were present in 20.1% and 12.3% of patients, respectively, while preoperative documented cardiovascular disease was uncommon (1.9%). Chronic hepatitis B infection was the predominant underlying liver disease, with 85.3% of patients positive for HBsAg and 49.4% having HBV DNA > 10^3 IU/mL (Supplementary Table S4, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*).

Overall liver function was relatively preserved. The mean Child-Pugh score was 5.1 ± 0.3, the median ALBI score was −2.8 (IQR, −3.1 to −2.6), and the mean MELD score was 7.6 ± 1.3. Cirrhosis was present in 57.0% of patients. The median tumor size was 5.0 cm (IQR, 3.0–7.5), single tumors were present in 85.2%, and microvascular invasion was identified in 28.6%. Most patients had BCLC stage 0 or A disease, while 7.3% had BCLC stage B disease (Supplementary Tables S4–S5, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*).

Regarding surgical characteristics, 25.0% of patients underwent major hepatectomy, 37.8% underwent anatomic hepatectomy, and 20.2% underwent laparoscopic hepatectomy. The median surgical duration was 205 minutes (IQR, 165–255), and the median intraoperative blood loss was 200 mL (IQR, 100–400). Hepatic inflow occlusion was performed in 82.9% of patients, with a median occlusion time of 34 minutes (IQR, 20–46) among those with available data (Supplementary Table S5, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*).

During the index hospitalization, 55.5% of patients experienced at least one postoperative complication, whereas 7.4% developed severe complications (Clavien-Dindo grade ≥ III). The median Comprehensive

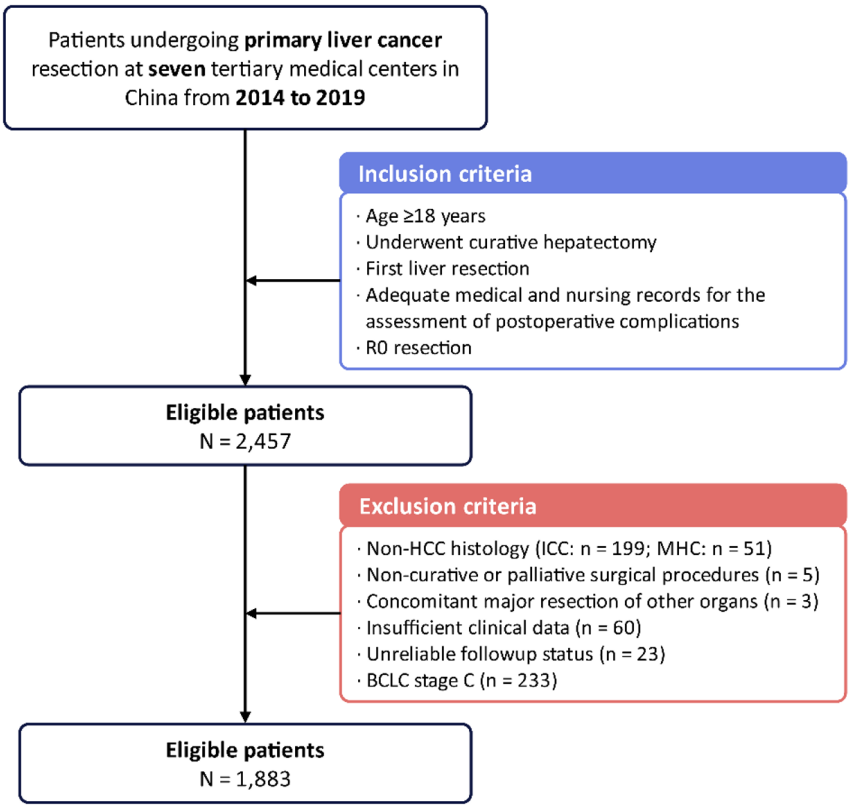

Figure 1. Patient selection and study design. Flowchart illustrates the inclusion and exclusion of patients undergoing primary liver cancer resection, resulting in the final study cohort.

Complication Index (CCI) was 8.7 (IQR, 0.0–17.4) (Table 1; Supplementary Figure S7, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*). Liver surgery-specific complications included bile leakage in 124 patients (6.6%), postoperative blood transfusion in 147 patients (7.8%), postoperative ascites in 48 patients (2.5%), PHLF in 46 patients (2.4%), and reoperation in 5 patients (0.3%). Cardiovascular complications included clinically significant arrhythmia in 120 patients (6.4%) and acute cardiac events in 45 patients (2.4%). Postoperative hemodynamic instability occurred in 126 patients (6.7%) and was recorded separately as an indicator of postoperative severity rather than as part of the cardiovascular complication composite. Thirty-day mortality occurred in 52 patients (2.8%), and 90-day mortality occurred in 118 patients (6.3%). The median length of hospital stay was 11 days (IQR, 8–16), with 505 patients (26.9%) classified as having prolonged hospitalization.

3.2. Postoperative complications and short-term clinical outcomes

Co-occurrence of postoperative complication domains was observed. At the domain level, 515 patients (27.3%) had one complication domain and 246 patients (13.1%) had two or more complication domains. Pairwise correlation analysis showed limited-to-moderate correlations among most postoperative complications, without evidence of strong collinearity across major domains (Supplementary Figure S5, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*). Therefore, subsequent PAF estimates were interpreted as domain-specific total burdens rather than mutually exclusive causal fractions. In multivariable analyses adjusting for demographic characteristics, comorbidities, liver function, tumor burden, and surgical factors (Model A), several postoperative complication domains were associated with adverse short-term outcomes. However, their relative contributions differed between 90-day mortality and prolonged hospitalization.

For 90-day mortality (Table 2; Supplementary Table S6, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*), liver surgery-specific complications accounted for the largest population-level burden (adjusted RR 1.61, 95% CI 1.08–2.40; adjusted PAF 10.0%, 95% CI 1.1–20.0). Cardiovascular complications were also strongly associated with 90-day mortality and represented the leading non-liver complication domain contributing to mortality at the population level (adjusted RR 2.21, 95% CI 1.40–3.50; adjusted PAF 9.4%, 95% CI 2.5–16.9). Renal complications (adjusted RR 3.00, 95% CI 1.51–5.94; adjusted PAF 4.0%, 95% CI 0.3–8.3) and pulmonary complications (adjusted RR 2.47, 95%

Table 1. Postoperative complications and adverse outcomes

Variables	No. (%)
Liver surgery-specific complications	
PHLF	46 (2.4%)
Bile leakage	124 (6.6%)
Postoperative ascites	48 (2.5%)
Postoperative blood transfusion	147 (7.8%)
Reoperation	5 (0.3%)
Cardiovascular complications	
Arrhythmia	120 (6.4%)
Acute cardiac events	45 (2.4%)
Pulmonary complications	63 (3.3%)
Renal complications	36 (1.9%)
Infection-related complications	
Incision infection	61 (3.2%)
Pulmonary infection	18 (1.0%)
Systemic infection	25 (1.3%)
Metabolic and electrolyte disorder	
Hypokalemia	7 (0.4%)
Hyperkalemia	51 (2.7%)
Hypoglycemia	278 (14.8%)
Hyperglycemia	30 (1.6%)
Gastrointestinal dysfunction	
Nausea and vomiting	93 (4.9%)
Diarrhea and constipation	20 (1.1%)
Indication of severity	
Escalation of care	22 (1.2%)
Postoperative hemodynamic instability	126 (6.7%)
Parenteral nutrition	3 (0.2%)
Mortality	
30-day	52 (2.8%)
90-day	118 (6.3%)
Hospitalization	
LOS (day)	11.0 [8.0, 16.0]
Prolonged hospital stay	505 (26.9%)
Clavien-Dindo grade	
0	838 (44.5%)
I	661 (35.1%)
II	245 (13.0%)
III	97 (5.2%)
IV	29 (1.5%)
V	13 (0.7%)
CCI	8.7 [0.0, 17.4]

Abbreviations: MASLD = Metabolic dysfunction-associated steatotic liver disease; PHLF = post-hepatectomy liver failure; CCI = Comprehensive complication index; LOS = Length of hospital stay.

CI 1.39–4.38; adjusted PAF 5.0%, 95% CI 0.2–10.1) were also associated with increased early mortality. In contrast, potassium imbalance, glucose dysregulation, and gastrointestinal dysfunction were not independently associated with 90-day mortality.

For prolonged hospitalization (Table 2; Supplementary Table S6, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*), liver surgery-specific complications had the greatest population-level impact (adjusted RR 1.65, 95% CI 1.41–1.93; adjusted PAF 11.0%, 95% CI 7.0–14.7). Among individual liver surgery-specific components, postoperative blood transfusion, postoperative ascites, and PHLF contributed meaningfully to prolonged length of stay. Several non-liver complications were also associated with prolonged hospitalization, including pulmonary complications (adjusted RR 2.29, 95% CI 1.88–2.78; adjusted PAF 4.8%, 95% CI 3.1–6.8), cardiovascular complications (adjusted RR 1.50, 95% CI 1.22–1.86; adjusted PAF 4.1%, 95% CI 1.5–6.7), renal complications (adjusted RR 1.78, 95% CI 1.29–2.46; adjusted PAF 1.9%, 95% CI 0.5–3.4), potassium imbalance (adjusted RR 2.22, 95% CI 1.80–2.75; adjusted PAF 4.3%, 95% CI 2.6–6.1), and glucose dysregulation (adjusted RR 1.26, 95% CI 1.04–1.53; adjusted PAF 4.5%, 95% CI 0.7–8.5).

Taken together, these findings indicate a divergence between hospitalization burden and mortality burden. This pattern was further illustrated in the population-level burden map (Figure 2), which integrated complication incidence, adjusted relative risk, and adjusted PAF for each complication domain. Liver surgery-specific complications showed the greatest population-level burden for prolonged hospitalization, whereas cardiovascular complications, despite a smaller contribution to prolonged length of stay, remained a major contributor to 90-day mortality.

3.3. Sensitivity analyses for short-term outcomes

Sensitivity analyses generally supported robustness of the main findings. For 90-day mortality, cardiovascular complications remained significantly associated with increased mortality across the tumor-burden-focused model, comorbidity-focused model, and surgery-focused model, with adjusted RRs ranging from 1.85 to 2.30 and adjusted PAFs ranging from 7.9% to 9.4%. Similar findings were observed after excluding patients with BCLC stage B disease, in whom cardiovascular complications remained associated with 90-day mortality, with an adjusted RR of 2.23 and an adjusted PAF of 8.7% (Supplementary Tables S7-S10, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*).

For prolonged hospitalization, liver surgery-specific complications consistently showed the greatest population-level burden across sensitivity analyses, with adjusted PAFs ranging from 10.9% to 12.2%. Cardiovascular complications were also consistently associated with prolonged hospitalization, but their adjusted PAFs were lower, ranging from 3.5% to 4.6% (Supplementary Tables S11-S14, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*).

3.4. Postoperative complications and long-term outcomes

The median follow-up duration, estimated using the reverse Kaplan–Meier method, was 36.4 months (IQR, 19.5–55.4 months). Recurrence-free survival analyses were conducted among 1,811 patients after exclusion of 72 individuals with missing recurrence data. During follow-up, 659 patients (35.0%) died, and 992 of 1,811 evaluable patients (54.8%) developed tumor

Table 2. Adjusted relative risks and population-attributable fractions of postoperative complications for 90-day mortality and prolonged length of stay

Variables	90-day mortality Relative Risk (95% CI)	90-day mortality Adjusted PAF (95% CI), %	P value	Prolonged LOS Relative Risk (95% CI)	Prolonged LOS Adjusted PAF (95% CI), %	P value
Liver surgery-specific complications	1.610 (1.082, 2.396)	10.0 (1.1, 20.0)	0.026	1.653 (1.413, 1.934)	11.0 (7.0, 14.7)	< 0.001
PHLF	2.341 (1.110, 4.938)	3.5 (-0.5, 7.8)	0.088	2.219 (1.766, 2.787)	3.5 (2.0, 5.1)	< 0.001
Bile leakage	1.578 (0.893, 2.788)	4.0 (-1.5, 10.2)	0.178	0.997 (0.754, 1.319)	-0.0 (-1.8, 2.0)	0.942
Postoperative ascites	1.737 (0.828, 3.646)	2.2 (-1.4, 6.2)	0.280	2.073 (1.664, 2.582)	3.6 (2.1, 5.3)	< 0.001
Postoperative blood transfusion	1.294 (0.759, 2.206)	2.6 (-3.1, 9.1)	0.414	1.730 (1.447, 2.067)	6.4 (3.8, 9.1)	< 0.001
Reoperation	2.472 (0.410, 14.917)	0.5 (-0.6, 2.3)	0.722	2.401 (1.493, 3.863)	0.5 (0.0, 1.1)	0.046
Other organs' complications						
Cardiovascular complications	2.209 (1.397, 3.495)	9.4 (2.5, 16.9)	0.008	1.504 (1.216, 1.860)	4.1 (1.5, 6.7)	< 0.001
Renal complications	2.998 (1.513, 5.940)	4.0 (0.3, 8.3)	0.030	1.780 (1.290, 2.456)	1.9 (0.5, 3.4)	0.010
Pulmonary complications	2.466 (1.389, 4.378)	5.0 (0.2, 10.1)	0.036	2.287 (1.883, 2.777)	4.8 (3.1, 6.8)	< 0.001
Infection-related complications						
Incision infection	1.609 (0.778, 3.329)	2.2 (-1.4, 6.8)	0.316	1.835 (1.440, 2.338)	2.9 (1.5, 4.6)	< 0.001
Pulmonary infection	3.236 (1.162, 9.013)	1.8 (-0.7, 4.9)	0.170	2.266 (1.652, 3.109)	1.3 (0.4, 2.5)	0.002
Systemic infection	1.726 (0.604, 4.934)	1.1 (-1.4, 4.2)	0.446	1.989 (1.306, 3.029)	1.3 (0.2, 2.4)	0.018
Metabolic and electrolyte disorder						
Potassium imbalance	0.736 (0.247, 2.189)	-1.0 (-3.5, 2.1)	0.492	2.223 (1.798, 2.748)	4.3 (2.6, 6.1)	< 0.001
Glucose dysregulation	1.196 (0.761, 1.881)	3.2 (-5.3, 12.0)	0.448	1.262 (1.044, 1.526)	4.5 (0.7, 8.5)	0.022
Gastrointestinal dysfunction	0.705 (0.292, 1.698)	-1.8 (-5.2, 2.6)	0.358	1.124 (0.838, 1.508)	0.7 (-1.2, 2.7)	0.492

Abbreviations: CI = Confidence Interval, PHLF = post hepatectomy liver failure. *Notes*: Models were adjusted for patient demographics (age, sex, BMI), comorbidities (diabetes, hypertension), liver disease severity (MELD score, cirrhosis), tumor burden (BCLC stage), and surgical characteristics (major resection, laparoscopic approach). Negative PAF estimates indicate no positive population-attributable burden under the fitted model and should not be interpreted as a protective effect.

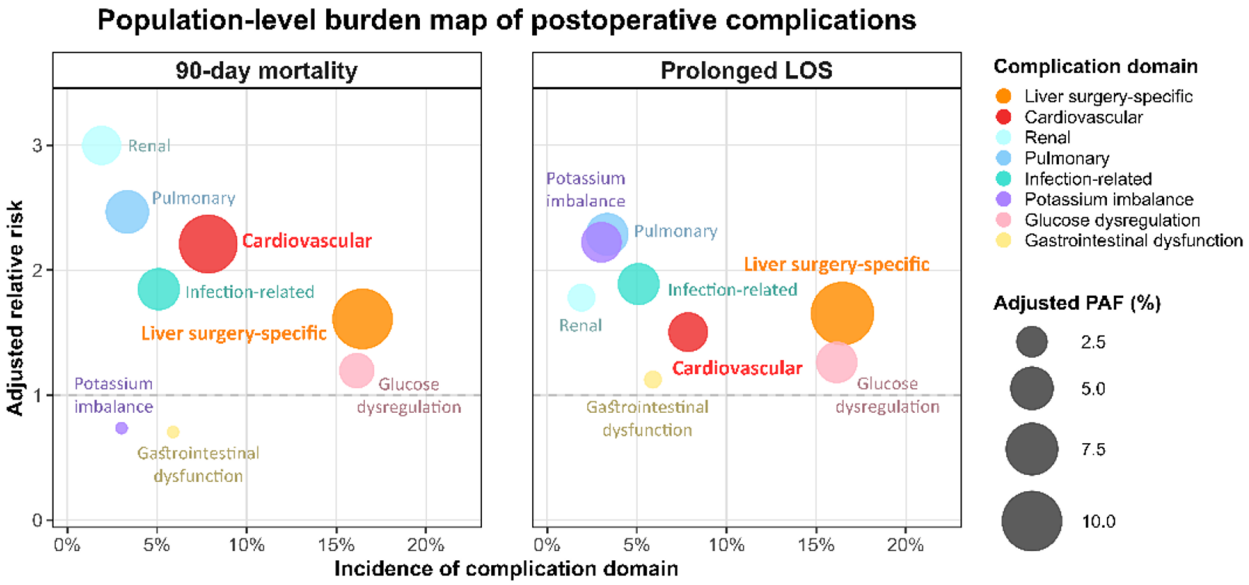

Figure 2. Population-level burden map of postoperative complications. Bubble plots showing the relationship between complication-domain incidence, adjusted relative risk, and adjusted population-attributable fraction (PAF) for 90-day mortality and prolonged length of stay. The x-axis represents the incidence of each complication domain, the y-axis represents adjusted relative risk, and bubble size represents adjusted PAF. Colors indicate complication domains. PAF estimates should be interpreted as domain-specific population-level burdens rather than mutually exclusive causal fractions.

recurrence. The 1-, 3-, and 5-year overall survival rates were 82.7%, 64.3%, and 45.5%, respectively, whereas the corresponding recurrence-free survival rates were 68.5%, 47.4%, and 38.3%. Kaplan–Meier curves stratified by BCLC stage are shown in Supplementary Figure S8 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*).

Kaplan–Meier analyses demonstrated poorer overall survival among patients with postoperative complications, whereas recurrence-free survival showed less pronounced separation between complication groups (Figure 3). In multivariable Cox models, several postoperative complication domains were independently associated with reduced overall survival, but no complication domain was independently associated with recurrence after adjustment (Figure 4; Supplementary Tables S15–S18, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=310*).

Specifically, pulmonary complications (adjusted HR 1.83, 95% CI 1.30–2.56), cardiovascular complications (adjusted HR 1.59, 95% CI 1.24–2.03), renal complications (adjusted HR 1.67, 95% CI 1.06–2.63), and glucose dysregulation (adjusted HR 1.34, 95% CI 1.09–1.65) were independently associated with worse overall survival. In contrast, no complication domain was independently associated with recurrence-free survival after adjustment.

4. Discussion

In this multicentre study of patients undergoing curative-intent hepatectomy for HCC, we applied a population-attributable fraction (PAF) framework to evaluate population-level impact of postoperative complications. The principal finding was a divergence between hospitalization burden and mortality burden. Liver surgery-specific complications contributed the greatest population-level burden of prolonged hospitalization, and also accounted for the largest PAF for 90-day mortality. However, cardiovascular complications represented the leading non-liver complication domain for 90-day mortality and remained strongly associated with worse long-term overall survival, despite contributing less to prolonged length of stay. No complication domain was independently associated with recurrence after adjustment. These findings suggest that postoperative complications may influence prognosis through distinct pathways, with liver surgery-specific complications mainly driving recovery burden, whereas cardiovascular complications may represent an underrecognized contributor to mortality risk.

Postoperative morbidity after hepatectomy has traditionally been evaluated using complication incidence, Clavien–Dindo grade, or individual relative risks. While these measures are clinically useful, they do not fully capture the population-level impact of different complication domains. A complication with a high relative risk but low incidence may contribute less to overall outcome burden than a more common complication with a moderate relative risk (*15*). The PAF framework provides a complementary perspective by integrating exposure frequency and relative risk, thereby helping prioritize complications according to their expected contribution to adverse outcomes at the

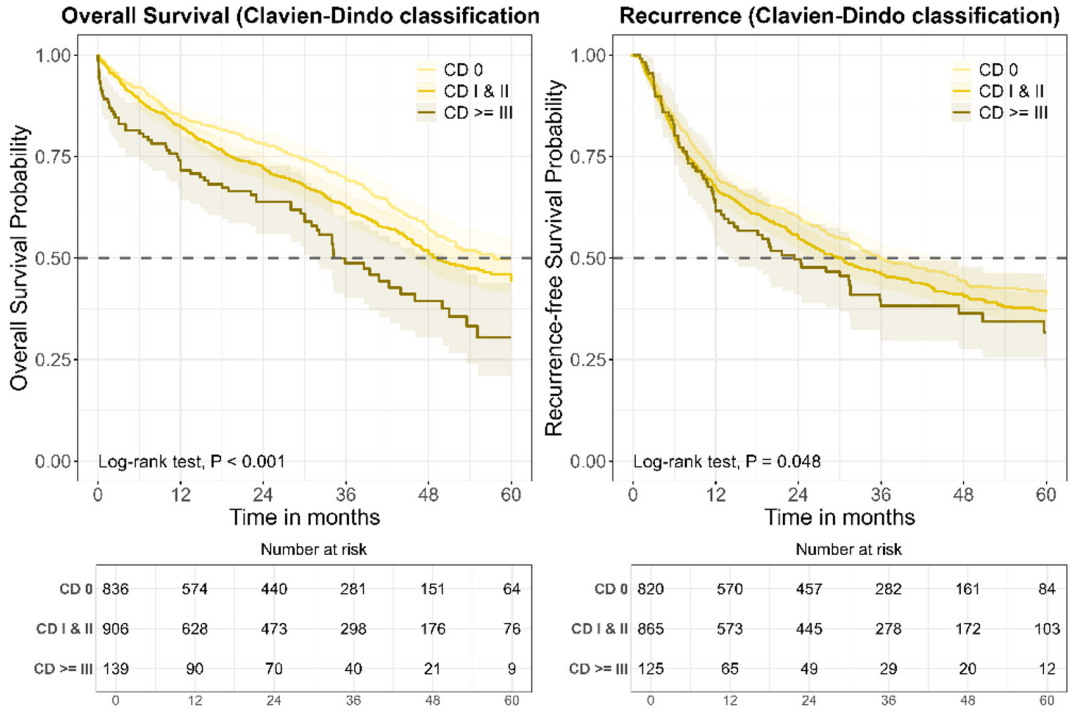

Figure 3. Overall survival and recurrence according to Clavien-Dindo classification. Kaplan-Meier curves showing overall survival (left panel) and recurrence-free survival probability (right panel) stratified by Clavien-Dindo post-operation complication classification (no complication, mild complication, and severe complication). Shaded areas represent 95% confidence intervals. The dashed horizontal line indicates the 50% probability level. Numbers at risk are shown below each plot. Differences between groups were assessed using the log-rank test.

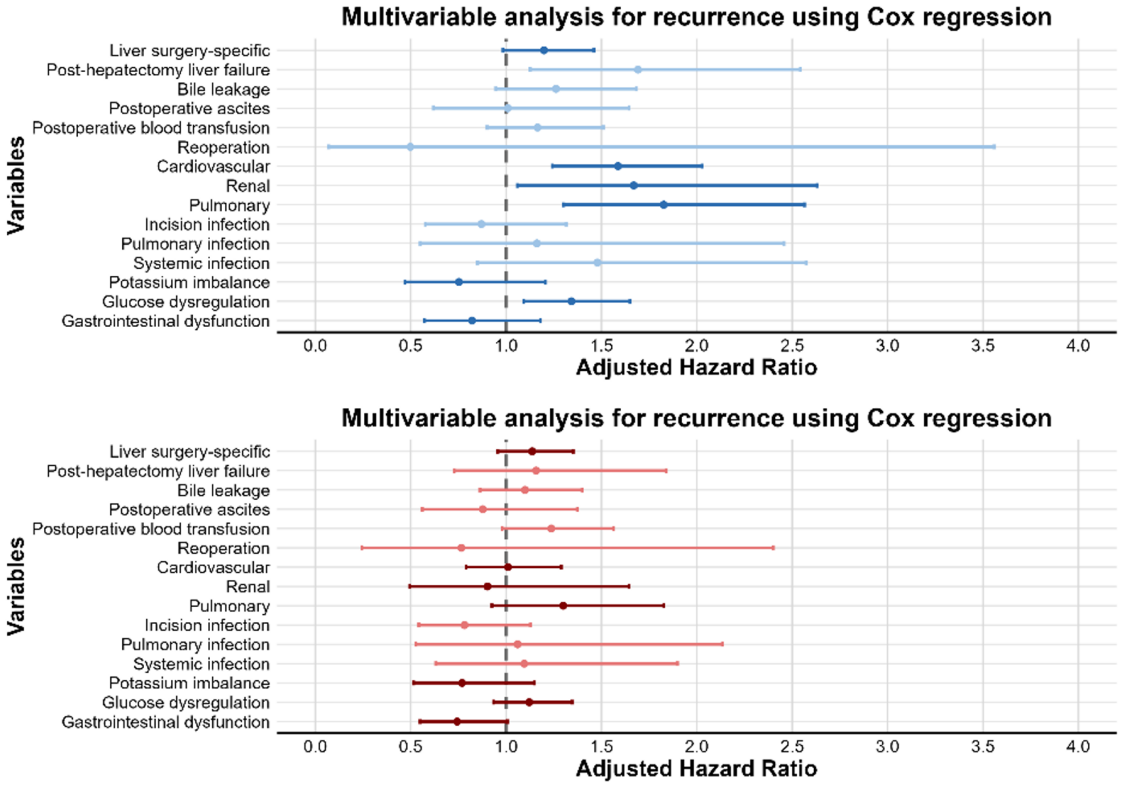

Figure 4. Adjusted associations between postoperative complications and long-term outcomes. Multivariable Cox regression analyses of postoperative complications in relation to overall survival (upper panel, blue) and recurrence (lower panel, red). Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) are shown. The vertical dashed line indicates an HR of 1.0. All models were adjusted for predefined clinically relevant covariates to minimize confounding. Based on prior literature and clinical relevance, models were adjusted for patient demographics (age, sex, body mass index), comorbidities (diabetes, hypertension), liver disease severity (MELD score and presence of cirrhosis), tumor burden (BCLC stage), and surgical characteristics (major resection and laparoscopic approach).

population level (*16-18*). In this study, this approach revealed that the apparent importance of complication domains depended on the outcome being considered: liver surgery-specific complications dominated prolonged hospitalization, whereas cardiovascular complications carried a substantial mortality burden despite a smaller impact on hospital stay.

This distinction has important clinical implications. Liver surgery-specific complications, such as PHLF, bile leakage, postoperative ascites, blood transfusion, and reoperation, are highly visible to hepatobiliary surgeons because they often require direct procedural, interventional, or liver-focused management and substantially prolong hospitalization (*19-21*). In contrast, cardiovascular complications may be less prominent in routine surgical outcome assessment if postoperative morbidity is judged mainly by length of stay or liver-specific adverse events (*22,23*). Nevertheless, our findings indicate that cardiovascular complications were the leading non-liver contributor to 90-day mortality and were independently associated with worse overall survival. This suggests a potential mismatch between clinical visibility and prognostic relevance: complications that most prolong hospital stay may not fully capture those most relevant to mortality risk.

The association between cardiovascular complications and mortality is biologically plausible, but should be interpreted within a broader perioperative vulnerability framework. Hepatectomy exposes patients to substantial physiological stress, including hemodynamic shifts, blood loss, fluid redistribution, inflammatory activation, sympathetic stimulation, and metabolic disturbance (*24-26*). In patients with limited cardiometabolic reserve, these stressors may precipitate clinically significant arrhythmia or acute cardiac events. Importantly, postoperative complications may not occur as isolated events. Some cardiovascular complications may develop secondary to other severe postoperative insults or share upstream causes such as bleeding, infection, liver dysfunction, inflammation, or systemic physiological stress (*27*). Therefore, the present findings should not be interpreted as proving a direct causal pathway from cardiovascular complications to mortality. Rather, cardiovascular complications may serve as clinically observable warning signals of systemic vulnerability and adverse postoperative trajectory.

This interpretation is clinically relevant because attention and resource allocation in surgical practice often follow complications that visibly require direct procedure-related management. In high-volume and highly specialized hepatobiliary centers, postoperative pathways are frequently oriented toward surgical recovery and bed turnover. Under such conditions, non-liver complications may be less visible within liver surgery-centered outcome assessment, even when they carry important prognostic implications. Our findings suggest that cardiovascular complications, despite contributing less to hospitalization burden than liver surgery-specific complications, identify a subgroup of patients with increased early mortality risk and worse long-term survival. The discordance between overall survival and recurrence-free survival is also informative. Absence of an independent association with recurrence-free survival further suggests that the long-term impact of postoperative complications may be driven more by systemic recovery and non-oncologic survival pathways than by tumor recurrence (*30*).

Our findings also support a broader shift from a purely technical liver surgery framework toward an integrated perioperative medicine framework. Modern hepatectomy outcomes are not determined solely by operative technique or liver-specific injury. They also reflect systemic vulnerability, including cardiometabolic reserve, renal function, pulmonary reserve, and the capacity to tolerate surgical stress (*28,29*). This is particularly relevant as the surgical population ages and the burden of metabolic and cardiovascular comorbidities increases. From this perspective, cardiovascular complications should not be viewed as peripheral events after hepatectomy, but as part of the systemic risk profile that shapes early mortality and long-term survival. Multidisciplinary perioperative pathways incorporating cardiovascular evaluation, intraoperative hemodynamic optimization, postoperative monitoring, and early recognition of cardiac events may therefore complement conventional liver-focused strategies.

Several strengths of this study deserve emphasis. First, this was a large multicentre cohort with detailed perioperative data and clinically meaningful short- and long-term endpoints. Second, complications were categorized using a predefined organ-system framework, allowing comparison of liver surgery-specific and non-liver complications within a unified analytic structure. Third, multiple imputations, robust regression models, bootstrap-based PAF estimation, and several sensitivity analyses were used to examine stability of the findings. The main results were generally consistent across tumor-burden-focused, comorbidity-focused, and surgery-focused adjustment strategies, as well as after excluding patients with BCLC stage B disease.

This study also has limitations. First, its retrospective design may introduce misclassification and residual confounding, although complications were adjudicated using predefined criteria and medical and nursing records. Second, organ-system grouping inevitably involves clinical judgment, and complications within the same domain may differ in severity, mechanism, and preventability. We, therefore, interpreted composite complication domains as indicators of system-level morbidity rather than as homogeneous biological entities. Third, PAF estimates rely on model-based counterfactual assumptions and should not be interpreted as proof that the corresponding complication could be fully eliminated in clinical practice. Instead, PAF was

used to compare relative population-level burden and to inform prioritization. Fourth, temporal relationships among postoperative complications could not be fully disentangled. Some complications may occur sequentially or share upstream causes, and future studies incorporating time-dependent or causal pathway analyses may further clarify these mechanisms. Finally, the cohort was derived from mainland China and was dominated by HBV-related HCC, so external validation in more diverse etiologic and healthcare settings is warranted.

In conclusion, this multicentre study shows that postoperative complications after hepatectomy exert distinct population-level effects on recovery and survival. Liver surgery-specific complications dominated prolonged hospitalization, but cardiovascular complications, despite being less prominent as drivers of hospital stay, emerged as the leading non-liver contributor to 90-day mortality and were independently associated with worse overall survival. These findings expose a blind spot in conventional liver surgery outcome assessment: complications that most visibly delay discharge are not necessarily those that carry greatest mortality relevance. Perioperative care after hepatectomy should therefore move beyond a liver-centric complication framework and incorporate systematic cardiovascular risk assessment and monitoring into routine surgical pathways for HCC.

Acknowledgements

The authors thank all participating centers, clinicians, and research staff for their contributions to data collection, clinical coordination, and patient care throughout this multicentre study.

Funding: This study was supported by grants from the Natural Science Foundation of Sichuan Province (2024NSFSC0637), the National Natural Science Foundation of China (82572143/82100650), and the National Key R&D Program of China (2022YFC2503701). The funding agency was not involved in the study design, data collection, analysis and interpretation, or writing of the manuscript and the decision to submit it for publication.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Data Availability Statement: Datasets generated during and/or analyzed during the current study are not publicly available due to patient privacy and institutional restrictions, but are available from the corresponding author on reasonable request.

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Received May 20, 2026; Revised July 10, 2026; Accepted July 24, 2026.

[§]These authors contributed equally to this work.
**Address correspondence to:*
Chuan Li, Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China.
E-mail: lichuan@scu.edu.cn

Released online in J-STAGE as advance publication July 31, 2026.