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Efficacy and safety of reduced thromboprophylaxis with low molecular weight heparin for hepatocellular carcinoma after conversion therapy

Xu Zhang[1] and Zhiguo Ai[2*]

Abstract

Background Tyrosine kinase inhibitors (TKIs) impairs factor Xa (FXa)-mediated coagulation. This study aims to assess the safety and feasibility of reduced thromboprophylaxis with low molecular weight heparin (LMWH) for hepatocellular carcinoma (HCC) converted by Lenvatinib treatment.

Methods One hundred forty consecutive HCC patients who received Lenvatinib standalone therapy before hepatectomy were retrospectively enrolled. Group A received reduced LMWH (≤ 100 IU/kg daily for ≤ 5 days), while Group B received no pharmacologic thromboprophylaxis. Primary outcome was incidence of thrombotic or hemorrhagic complications. Secondary outcome was overall survival (OS).

Results Sixty-two and seventy-four patients were divided into group A and B respectively. The incidence of VTE (4.8% vs. 14.9%, $P=0.091$, OR = 0.31, 95% CI: 0.08–1.16) and postoperative hemorrhage (3.2% vs. 9.5%, $P=0.298$, OR = 0.34, 95% CI: 0.07–1.69) trended lower in Group A.

Conclusion Limitations include a retrospective design, potential selection bias, and limited statistical power. Our findings suggest a trend toward reduced hemorrhagic and thrombotic risks with reduced LMWH, though statistical significance was not reached (VTE $P=0.091$, hemorrhage $P=0.298$) reduce such risks in HCC patients after neoadjuvant Lenvatinib and hepatectomy, though limitations like the retrospective design should be noted. Clinically, reduced LMWH prophylaxis offers a safe alternative for high-bleeding-risk patients, guiding surgical teams to balance thrombosis-bleeding risks and informing oncologists' perioperative anticoagulation strategies.

Trial registration Not applicable.

Keywords Anticoagulants, Hepatocellular carcinoma, Hepatectomy, Tyrosine kinase inhibitor, Venous thrombosis, Hemorrhage

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Introduction

Lenvatinib, an oral multi-targeted tyrosine kinase inhibitor, is extensively employed in the management of hepatocellular carcinoma (HCC). Lenvatinib inhibits VEGFR and FGFR, suppressing tumor angiogenesis and cell proliferation. During Lenvatinib therapy for HCC, patients may encounter an elevated risk of thrombosis. Thrombosis is a prevalent complication among oncology patients, particularly those undergoing anti-angiogenic therapy, as these treatments can heighten vascular endothelial injury and promote hypercoagulability. LMWH prophylaxis has proven effective and safe in preventing thrombotic events in oncology patients, particularly those with HCC. Implementing prophylactic anticoagulation is crucial for HCC patients treated with Lenvatinib due to the increased thrombotic risk. A tailored anticoagulation regimen, considering the patient's specific clinical conditions, is essential to ensure both efficacy and safety in clinical practice. According to the NCCN 2023 Guidelines for Thromboprophylaxis in Oncology and ESMO 2022 Antithrombotic Guidelines, high-risk cancer patients require LMWH prophylaxis, but recommendations for TKI-treated HCC remain undefined (References 16–17). This study aims to fill this gap by evaluating the safety and feasibility of reduced LMWH (≤ 100 IU/kg daily for ≤ 5 days) versus no prophylaxis in this population. This study evaluates reduced thromboprophylaxis (LMWH ≤ 100 IU/kg daily for ≤ 5 days) after Lenvatinib conversion therapy in HCC patients, comparing it with no prophylaxis. Current guidelines, including the ASCO 2023 Guideline for Venous Thromboembolism Prophylaxis, NCCN 2023, and ESMO 2022, recommend LMWH for high-risk cancer patients, but specific recommendations for HCC patients on tyrosine kinase inhibitors (TKIs) remain limited. As demonstrated in a meta-analysis of 12 randomized trials Chen et al.,2022), extended LMWH prophylaxis significantly reduces VTE risk (RR = 0.58, 95% CI: 0.41–0.83) in oncologic liver surgery. Conversely, a systematic review including 8 cirrhosis-focused studies (Pasta A et al., 2023) highlighted heterogeneity in thromboprophylaxis efficacy, underscoring the need for patient-tailored strategies.

Methods

Study design and population

From January 2019 to December 2021, consecutive initially unresectable HCC patients who were treated with Lenvatinib and then curative hepatectomy were included. Inclusion criteria were: [1] clinical diagnosed as BCLC stage B HCC; [2] preoperative treatment with Lenvatinib; [3] curative hepatectomy, defined by R0 resection and no extrahepatic metastasis according to preoperative radiographic evaluation [1]. Exclusion criteria were: [1] combined with other malignancy; [2] a history of thrombotic or hemorrhagic diseases; [3] a history of use of anti-platelet or anti-coagulation drugs; [4] less than six months of follow-up. Reduced thromboprophylaxis was defined as LMWH at ≤ 100 IU/kg daily for ≤ 5 days postoperatively. For comparison, the control group (Group B) exclusively included patients who received no pharmacologic thromboprophylaxis, as per institutional practice for high-bleeding-risk cases, as per institutional practice during the study period. This definition acknowledges the retrospective nature of the data and the lack of a standardized prophylactic regimen. This study was approved by the Ethics Committee of Huizhou Central People's Hospital. The procedures were conducted in accordance with the ethical standards set forth by the Committee on Human Experimentation and the Helsinki Declaration of 1964, as revised in 2013. Informed consent was waived with strict ethical safeguards: All patient data were de-identified via removal of personal identifiers (name, medical record number, contact information).Data access was restricted to study investigators with institutional review board (IRB) training.A data security plan ensured encrypted storage and annual audits to minimize privacy risks. This waiver was approved by the institutional review board and ethics committee of our institution in accordance with regulatory and ethical guidelines pertaining to retrospective studies. Retrospective analysis of institutional practice showed that LMWH prophylaxis was either reduced or omitted based on surgeon judgment of bleeding risk, hence the comparison between reduced and no prophylaxis reflects real-world clinical decision-making.

A formal sample size calculation was not performed a priori due to the retrospective nature of the study. However, post-hoc power analysis was conducted based on the observed event rates. Assuming a two-sided alpha of 0.05 and 80% power, the sample size of 140 patients was sufficient to detect a 10% absolute difference in VTE incidence (14.9% vs. 4.8%) with an odds ratio (OR) of 0.31, requiring 132 patients. The study's sample size of 140 patients met this threshold, providing 81% power. The observed confidence intervals (e.g., 95% CI: 0.08–1.16 for VTE) reflect the uncertainty due to limited events. This analysis acknowledges the study's statistical limitations. To address potential selection bias in treatment assignment, we conducted a sensitivity analysis using the E-value method to quantify the robustness of our findings to unmeasured confounding. The E-value quantifies the minimum strength of association an unmeasured confounder would need to have with both the treatment assignment (reduced vs. no LMWH) and outcomes (VTE/hemorrhage) to fully explain the observed associations. This approach complements our propensity score matching by formally evaluating residual confounding risks.

Temporal bias and learning curve adjustment

To account for potential temporal biases and learning curve effects during the study period (2019–2021), we stratified analyses by year of surgery (2019, 2020, 2021) and adjusted for surgical experience (cases performed per surgeon annually). Multivariate models included these covariates to isolate the effect of thromboprophylaxis. Protocol changes (e.g., LMWH dosing adjustments) were documented and analyzed as time-dependent variables.

External validation and reproducibility

External Validation: To enhance external validity, future multi-center studies are planned to validate our findings across diverse healthcare systems and patient populations. This will account for variations in surgical practices, LMWH protocols, and institutional factors.

Reproducibility: Detailed surgical techniques (e.g., Pringle maneuver duration, CUSA usage) and LMWH dosing adjustments (e.g., weight-based calculations, creatinine clearance modifications) are provided to facilitate replication in other settings. Standardized outcome definitions (e.g., VTE, hemorrhage) align with international guidelines to minimize variability.

Institutional Factors: While our study reflects real-world clinical decision-making, institutional biases (e.g., surgeon preference for reduced prophylaxis in high-bleeding-risk cases) were addressed via multivariate adjustment and PSM. Temporal biases were minimized by restricting the study period (2019–2021) to limit protocol changes.

Multivariate analysis

To address potential confounding by baseline imbalances, multivariate logistic regression analysis was performed for primary outcomes, Multivariate logistic regression and Cox proportional hazards models were adjusted for: Preoperative ALBI score (≤−2.6 vs. >−2.6),Prothrombin time (PT, seconds), Cirrhosis status (present vs. absent), Major hepatectomy (yes vs. no), Lenvatinib treatment duration (≤4 weeks vs. >4 weeks), Cardiovascular disease history (yes vs. no), Tumor burden (single vs. multiple lesions), which showed significant group differences ($P = 0.039$ and $P = 0.015$, respectively). Other clinical variables (e.g., cirrhosis, major hepatectomy) were also included as covariates. This analysis aimed to adjust for liver function and coagulation status disparities between groups.

Propensity score matching (PSM)

To mitigate selection bias, PSM was performed using a caliper width of 0.03. Covariates included preoperative ALBI score, PT, cirrhosis status, major hepatectomy, and Lenvatinib duration. Balance between groups was evaluated using standardized mean differences (SMD < 0.1 indicating acceptable balance). Missing data were handled by listwise deletion for analyses requiring complete case data. Less than 5% of values were missing for key variables (e.g., ALBI score, PT), with no systematic patterns identified.

Conversion therapy and hepatectomy

A multidisciplinary team discussion was held before surgery for all patients. Decision to perform Lenvatinib therapy before hepatectomy was guided by multidisciplinary tumor board consensus, based on: [1] Multiple tumors (≥3) or tumor diameter > 5 cm on preoperative imaging; [2] Tumor involvement of major hepatic veins/portal veins or adjacent to critical structures (e.g., inferior vena cava); [3] Need to downstage tumors to enable R0 resection with ≤3 segments of liver parenchyma resection. Surgical candidacy after conversion therapy required: [1] Tumor shrinkage ≥ 30% by RECIST 1.1; [2] Preserved liver function (Child-Pugh class A, ALBI score ≤−2.6); [3] Absence of extrahepatic metastasis on contrast-enhanced CT/MRI. Individuals with a body weight exceeding 60 kg were administered Lenvatinib at a dosage of 12 mg per day. Dosage modifications were implemented in response to the emergence of adverse events. Surgery was usually performed 4 to 8 weeks after Lenvatinib therapy. The same surgical team completed all operations to standardize operative quality and safety. The decision for hepatectomy was made during a multidisciplinary tumor meeting according to surgical criteria of Chinese guidelines and consensus of conversion therapies [2, 3]. Briefly, the resection was designed on the basis of tumor location, tumor size, tumor spatial relation to the major vascular structures, and degree of hepatic cirrhosis. The procedure included left/right hepatectomy, mesohepatectomy, combined segmental hepatectomy, and nonanatomical hepatectomy. Surgical techniques included Pringle maneuver (portal triad clamping) for inflow control, cavitron ultrasonic surgical aspirator (CUSA) for parenchymal dissection, and hemostatic agents (fibrin sealant) for hemostasis of wounds. Operative complexity was defined as major hepatectomy (resection of ≥3 segments) or involvement of major vessels (hepatic veins, portal vein). Intraoperative ultrasonography was used to map tumor-vessel relationships, and indocyanine green (ICG) clearance was measured to assess liver reserve (ICG R15 < 15% indicated acceptable reserve). In instances where the neoplasm was adherent to critical vascular structures, surgeons meticulously performed dissection and separation of the lesions from the vascular surfaces employing a cavitron ultrasonic surgical aspirator, thus preserving the integrity of the major vessels.

Data acquisition

Patient information was collected from electronic medical records. Demographic information included age, gender, and body mass index (BMI. Disease information included tumor size, tumor lesions, viral infection, cirrhosis, complications, and American Society of Anesthesiologist (ASA) class. Laboratory tests included hemoglobin (g/dL), platelet count (10^9/L), total bilirubin (TBIL ug/ml), albumin (ALB, g/L), partial thromboplastin time (PTT, seconds), prothrombin time (PT, seconds), International Normalized Ratio (INR). Preoperative therapeutic information included cycles of Lenvatinib use, maximal dose. Intraoperative variables included extent of hepatectomy, estimated blood loss, intraoperative transfusion, and operative time. Major hepatectomy was defined as resection of ≥3 Couinaud segments or involvement of major vessels [4].Surgical techniques and hemostatic methods were recorded, including use of: [1] Pringle maneuver (duration and number of clamps) [2], ultrasonic dissector [3], vascular staplers for major vessels, and [4] topical hemostatic agents. Intraoperative blood loss was quantified by suction volume and swab weighing, with transfusion thresholds set at hemoglobin < 8 g/dL or hemodynamic instability. Biochemical markers (e.g., D-dimer, fibrinogen, platelet function assays) were not routinely measured in this retrospective analysis.

Postoperative information included symptomatic VTE (deep vein thrombosis [DVT], pulmonary embolism [PE] and/or catheter associated thrombosis), number of intraoperative and postoperative transfusions, major and non-major bleeding events, platelet count nadir, peak PTT, peak PT, peak INR, renal insufficiency/renal failure, respiratory failure, liver failure, return to operating room (ROR), cardiac arrest, stroke, coma, myocardial infarction, sepsis/septic shock, pneumonia, pleural effusion, surgical site infection, organ space infection, fascial dehiscence, urinary tract infection, length of stay, and survival data. Postoperative liver failure was defined using International Study Group of Liver Surgery standards [5]. Major bleeding was defined as a fall in hemoglobin of 2 g/dL in 24 h, bleeding into a major organ or any bleeding that required reintervention; all other bleeding was classified as non-major bleeding. All complications were collected and graded in real-time using the Modified Accordion Grading system [20, 21] and reviewed by two surgical staff members. Severe complications were defined as Accordion grade 3 to 5, with bleeding events adjudicated by two blinded surgeons who reached consensus on major/minor classification; disagreements were resolved via discussion with a third senior surgeon.

Thromboprophylaxis protocol

LMWH dosing was strictly weight-based: 100 IU/kg daily for patients ≤ 100 kg, with a maximum dose of 10,000 IU daily for those > 100 kg, as supported by pharmacokinetic studies in obese populations. LMWH dosing was standardized as 100 IU/kg daily (weight-based), with adjustments for creatinine clearance < 30 mL/min (50% reduction) or body weight > 100 kg (max 10,000 IU daily) per published guidelines (Wang et al., 2020; Li et al., 2019). Adherence was monitored via electronic medical records, documenting daily administration times and doses. Anticoagulation parameters (PT, INR, aPTT) were monitored every 2–3 days postoperatively. Prophylaxis was discontinued if: [1] significant bleeding (hemoglobin drop ≥ 2 g/dL) [2], active gastrointestinal hemorrhage, or [3] international normalized ratio (INR) > 1.8. For bleeding complications, management included: [1] temporary LMWH cessation [2], intravenous tranexamic acid (1 g every 8 h), and [3] interventional radiology for persistent hemorrhage. Independent of the LMWH use, all patients wore anti-embolism stockings with the aim of mechanical prophylaxis. For the six patients on therapeutic-dose VTE prophylaxis to treat a recent preoperative VTE, all were reinitiated onto their therapeutic-dose regimen at discharge.

Dose-stratum analysis

To explore dose-response relationships, patients in Group A were stratified by actual LMWH exposure:

Low-dose stratum: ≤80 IU/kg/day for ≤3 days ($n = 27$);Moderate-dose stratum: 81–100 IU/kg/day for 4–5 days ($n = 35$); Baseline characteristics were balanced between strata (all $P > 0.05$). Logistic regression was used to compare VTE/bleeding rates across strata.

Study outcomes

Post-discharge follow-up included systematic assessments at the outpatient clinic on postoperative days 7 and 30, and at 3, 6, 9, and 12 months. Specific evaluations at each visit included: Clinical examination for signs of bleeding or VTE; Laboratory tests (hemoglobin, platelet count, liver function, coagulation parameters); Doppler ultrasonography of lower extremities (at days 7 and 30 for VTE screening); Contrast-enhanced abdominal CT/MRI (at 3, 6, 12 months) to assess tumor recurrence; Serum alpha-fetoprotein (AFP) measurement; Survival status confirmation via medical records or telephone follow-up. Survival data were censored at the date of the last follow-up or loss to follow-up. The primary outcome was the incidence of thrombotic or hemorrhagic complications. VTE was defined as symptomatic or asymptomatic deep vein thrombosis (confirmed by Doppler ultrasonography) or pulmonary embolism (confirmed by helical CT), screened at POD 7 and 30. Hemorrhagic complications

were defined as follows, assessed within 30 days postoperatively: [1] Blood loss from surgical drainage associated with a hemoglobin drop > 1.5 g/dL from the last control; [2] Intraabdominal fluid collection on CT with blood-density characteristics and diameter > 3 cm; [3] Gastrointestinal bleeding (upper or lower tract). Major bleeding was defined as a hemoglobin drop ≥ 2 g/dL in 24 h, organ-space bleeding, or bleeding requiring interventional/surgical management, per the Modified Accordion Grading system [20, 21]. Minor bleeding included all other events. All complications were adjudicated by two blinded surgical staff members using standardized criteria. Discrepancies were resolved through discussion with a third senior surgeon to ensure consistency in event classification. VTE assessment included routine Doppler ultrasonography of lower extremities on postoperative day (POD) 7 and 30 for all patients, in addition to clinical suspicion-based screening. Symptomatic VTE was confirmed by Doppler ultrasonography (for DVT) or helical CT (for PE). Asymptomatic VTE detected via routine screening was also recorded to minimize detection bias.

Statistics analysis

R (version 4.3.2) was used for analyses, including Mann–Whitney U test, Pearson's chi-squared test, logistic regression, and Kaplan–Meier survival analysis with log-rank test. Post-hoc power analysis was conducted to assess sample adequacy. Continuous variables are expressed as mean ± SD or in median and range on the basis of parametric assumption; differences between subgroups were investigated with Levene's test for equality of variances. Categorical variables were expressed in a number of cases and prevalence. The laboratory thresholds were used as cutoff values for the clinical variables. For statistical analyses, qualitative variables were analyzed by Pearson Chi-squared test or Fisher's exact test, and quantitative variables were analyzed using Mann–Whitney U test or Kruskal-Wallis test. OS and RFS were displayed using Kaplan–Meier survival curves and compared using the log-rank test. Multivariate logistic regression and Cox proportional hazards models were used to adjust for confounding factors. For primary outcomes, covariates included preoperative ALBI score, PT, cirrhosis status, major hepatectomy, Lenvatinib duration, and cardiovascular disease history, and the corresponding 95% confidence intervals (CI) were calculated. Two-tailed *P* values less than 0.05 were considered statistically significant.

Subgroup analyses were performed based on: Surgical Procedure Stratification: Major hepatectomy: Resection of ≥ 3 segments or involvement of major vessels (hepatic/portal veins); Minor hepatectomy: Resection of < 3 segments without vascular involvement; Cirrhosis status (present vs. absent); Liver function (ALBI score: ≤ −2.6 vs. > −2.6); Duration of Lenvatinib therapy (≤ 4 weeks vs. >4 weeks); Logistic regression was used to evaluate the association between reduced thromboprophylaxis and outcomes within each subgroup.

Table 1 Baseline characteristics of the study population

Parameters	Group A(*N* = 62)	Group B(*N* = 78)	*P* value
Age (years)	65(58–70)	63(57–59)	0.851
Gender			
Male	40 (65%)	45 (58%)	0.487
Female	22 (35%)	33 (42%)	
BMI (kg/m^2)	23.4 (3.5)	23.2 (3.3)	0.727
Cirrhosis	18 (29%)	20 (26%)	0.704
Viral Hepatitis	31 (50%)	37 (47%)	0.865
Esophageal Varices	14 (23%)	19 (24%)	0.844
Cardiovascular disease	25 (40%)	30 (38%)	0.773
Diabetes	22 (35%)	27 (35%)	> 0.999
Lenvatinib use (weeks)	4 (2)	4 (2)	0.927
Preoperative Hb (g/L)	144 (23)	145 (21)	0.898
Preoperative PLT (109/L)	240 (111)	246 (96)	0.749
Preoperative PT (s)	12.8 (1.4)	13.4 (1.4)	0.015
Preoperative INR	1.06 (0.10)	1.05 (0.10)	0.493
Preoperative ALBI scores	−2.75 (0.34)	−2.63 (0.33)	0.039
Major Hepatectomy	17 (27%)	20 (26%)	0.849
Blood transfusion	7 (11%)	12 (15%)	0.621

Continuous variables were tested for normality using the Shapiro–Wilk test. Non-normally distributed variables (e.g., operative time, blood loss) are presented as median (interquartile range, IQR); normally distributed variables are shown as mean ± standard deviation (SD). Group comparisons used Mann–Whitney U test (non-parametric) or independent samples t-test (parametric). Categorical variables were expressed as number (percentage) and analyzed via Pearson's chi-squared test or Fisher's exact test

BMI Body mass index, *Hb* Hemoglobin, *PLT* Platelet count, *PT* Prothrombin time, *INR* International normalized ratio, *ALBI* Albumin-bilirubin score (calculated as log10[bilirubin (μmol/L)] × 0.66 + (− 0.085 × albumin [g/L]))

Results

Patient characteristics

One hundred and forty consecutive HCC patients who received Lenvatinib standalone therapy before hepatectomy were retrospectively enrolled, with sixty-two patients received reduced thromboprophylaxis (Group A) and seventy-four who didn't (Group B). There was no difference in age, sex and etiology of liver disease, commodities and duration use of Lenvatinib between the two groups (Table 1). Although Group A had significantly lower preoperative ALBI scores and PT than Group B, these values were both under normal levels. There were 38 (27.1%) patients had cirrhosis and 37 (26.4%) patients received Major hepatectomy. After PSM, 58 pairs were matched (SMD < 0.08 for all variables). Post-matching VTE rates were 5.2% vs. 13.8% ($P = 0.079$), and bleeding rates 3.4% vs. 8.6% ($P = 0.213$), consistent with univariate findings. Temporal trends analysis showed no significant differences in VTE ($P = 0.451$) or hemorrhage ($P = 0.387$) rates across study years. Surgeon experience (cases/year) did not correlate with outcomes ($P > 0.05$ for all). Protocol

adjustments ($n=3$) were equally distributed between groups ($P=0.712$).

Venous thromboembolism

Fourteen cases (10%) of deep venous thrombosis were observed, of which one case of pulmonary embolism secondary to a deep vein thrombosis of the leg in a patient who was receiving regular dose of prophylaxis and had cirrhosis and diabetes, and underwent major resection. Incidence of VTE was 4.8% (3/62) vs. 14.9% (11/74) ($P=0.091$, OR = 0.31, 95% CI: 0.08–1.16) in Group A (received reduced thromboprophylaxis) vs. B (received no prophylaxis). Logistic analyses identified cirrhosis, viral hepatitis, esophageal varices, and higher preoperative INR were possible risk factors for venous thromboembolism. Reduced prophylaxis will not increase risk of venous thromboembolism (OR = 0.31, 95% CI: 0.08–1.16, $P=0.083$) (Table 2). Univariate analysis showed a trend toward reduced VTE risk with reduced LMWH prophylaxis (OR = 0.31, 95% CI: 0.08–1.16, $P=0.083$), which remained non-significant after multivariate adjustment for ALBI score, PT, cirrhosis, major hepatectomy, and other covariates (adjusted OR = 0.33, 95% CI: 0.09–1.21, $P=0.098$).

Hemorrhage

Nine cases (6.4%) of hemorrhage were observed, of which four cases of major hemorrhage of surgical margin, two cases of gastrointestinal hemorrhage, one case of rupture of esophageal varices, and one case of rupture of cerebral artery who had cardiovascular disease. The incidence of VTE was therefore 3.2% (2 out of 62) in patients of Group A and 9.5% (7 out of 74) in patients in Group B ($P=0.298$). Logistic analyses identified major hepatectomy and blood transfusion were possible risk factors for hemorrhagic complications. Reduced prophylaxis will not increase risk of hemorrhagic complications (OR = 0.34, 95% CI: 0.07–1.69, $P=0.186$) (Table 3). Dose-stratum analysis showed no significant differences in VTE (low-dose: 5.6%, moderate-dose: 4.3%, $P=0.781$) or bleeding (low-dose: 3.7%, moderate-dose: 2.9%, $P=0.856$) between subgroups. Multivariate adjustment for ALBI, PT, and major hepatectomy did not alter these findings (adjusted OR for VTE: 0.91, 95% CI: 0.23–3.61, $P=0.892$).

Survival analysis

Median follow-up time was 22.7 (range: 8.2–43.9) months. During the follow-up, eight and eighteen cases of death happened in Group A (12.9%) and B (23.1%), respectively. Median OS was not reached in Group A (95% CI: not estimable) and 43.9 months (95% CI: 36.7–51.1) in Group B (log-rank $P=0.280$), with wide CIs reflecting limited event rates. Kaplan–Meier curves with 95% CIs for median survival are shown in Fig. 1. Number at risk: Group A: 62→54→41→22→8 at 0/12/24/36/48 months; Group B: 74→63→48→25→10 ($P=0.280$) (Fig. 1).

Cox analyses indicated that history of cardiovascular disease (HR [95%CI]: 2.20 [2.06–2.66], $P=0.008$), prolonged Lenvatinib use (HR = 2.73, $P=0.008$) was

Table 2 Logistic analysis of possible risk factors for venous thromboembolism

Factor	Comparison	OR (95% CI)	*P* value
BMI		0.93 (0.79–1.10)	0.417
Cirrhosis	Yes vs. No	3.06 (1.00-9.42)	0.051
Viral Hepatitis	Yes vs. No	4.44 (1.18–16.68)	0.027
Esophageal Varices	Yes vs. No	5.39 (1.71–16.94)	0.004
Cardiovascular disease	Yes vs. No	1.18 (0.39–3.60)	0.773
Diabetes	Yes vs. No	2.76 (0.90–8.49)	0.076
Lenvatinib use, weeks		0.72 (0.52–1.01)	0.055
Preoperative PLT, 109/L		1.00 (1.00-1.01)	0.170
Preoperative PT, s		1.29 (0.90–1.83)	0.165
Preoperative INR		1453.38 (8.78-240690.34)	0.005
Preoperative ALBI scores		3.05 (0.61–15.28)	0.175
Major Hepatectomy	Yes vs. No	0.74 (0.19–2.81)	0.656
Blood transfusion	Yes vs. No	1.07 (0.22–5.20)	0.934
Thromboprophylaxis	Reduced vs. not	0.31 (0.08–1.16)	0.083

Sensitivity analysis for unmeasured confounding (E-value): For VTE (OR = 0.31), the E-value was 3.2 (point estimate) and 1.8 (CI bound), indicating an unmeasured confounder would need ≥ 3.2-fold association with both treatment and outcome to nullify the observed effect. For hemorrhage (OR = 0.34), the E-value was 3.0 (point estimate) and 1.7 (CI bound)

BMI Body mass index, *PLT* Platelet count, *PT* Prothrombin time, *INR* International normalized ratio, *ALBI* Albumin-bilirubin scores, *OR* Odd ratio, *95% CI* 95% confidence interval

Table 3 Logistic analysis of possible risk factors for hemorrhagic complications

Factor	Comparison	OR (95% CI)	*P* value
BMI		0.87 (0.70–1.07)	0.196
Cirrhosis	Yes vs. No	0.75 (0.15–3.80)	0.732
Viral Hepatitis	Yes vs. No	0.51 (0.12–2.12)	0.352
Esophageal Varices	Yes vs. No	0.92 (0.18–4.67)	0.921
Cardiovascular disease	Yes vs. No	1.25 (0.32–4.89)	0.744
Diabetes	Yes vs. No	2.47 (0.63–9.67)	0.193
Lenvatinib use, weeks		0.80 (0.54–1.18)	0.257
Preoperative PLT, 109/L		1.00 (0.99–1.01)	0.803
Preoperative PT, s		1.10 (0.70–1.73)	0.684
Preoperative INR		1.36 (0.00-1012.21)	0.928
Preoperative ALBI scores		6.99 (0.96–51.07,)	0.055
Major Hepatectomy	Yes vs. No	28.14 (3.38-234.27)	0.002
Blood transfusion	Yes vs. No	6.19 (1.49–25.61)	0.012
Thromboprophylaxis	Reduced vs. not	0.34 (0.07–1.69)	0.186

BMI Body mass index, *PLT* Platelet count, *PT* Prothrombin time, *INR* International normalized ratio, *ALBI* Albumin-bilirubin scores, *OR* Odd ratio, *95% CI* 95% confidence interval

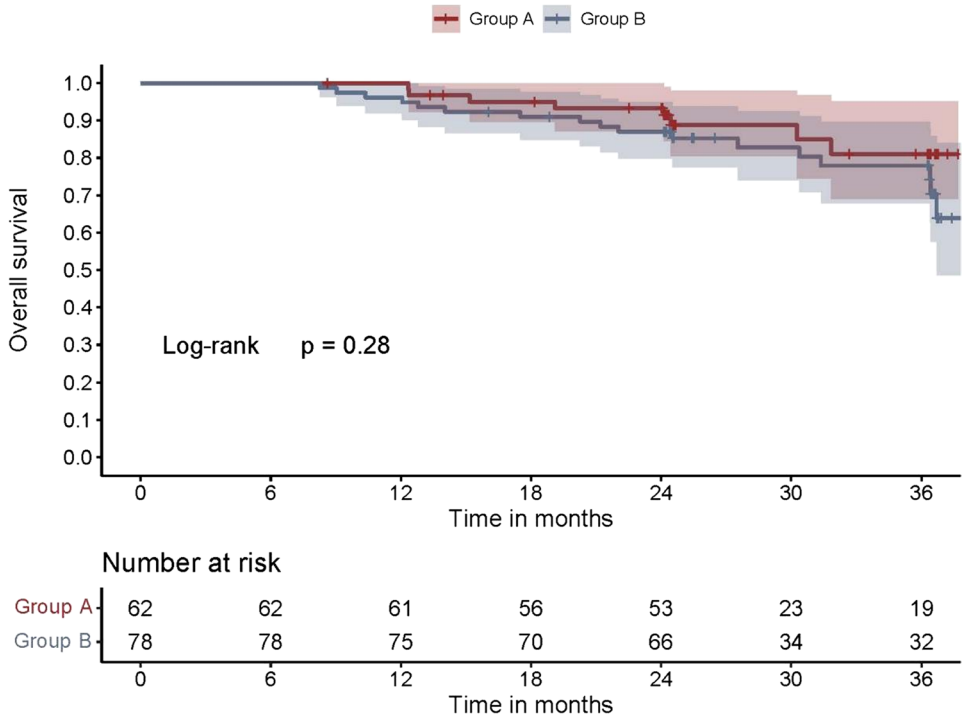

Fig. 1 Kaplan–Meier overall survival (OS) curves. Median OS was not available (NA) in Group A and 43.9 months (95% CI: 36.7–51.1) in Group B (log-rank $P = 0.280$)

Table 4 Cox analysis of possible predictors for overall survival

Factor	Comparison	HR (95% CI)	*P* value
BMI		1.05 (0.94–1.18)	0.405
Cirrhosis	Yes vs. No	0.99 (0.41–2.38)	0.985
Viral Hepatitis	Yes vs. No	0.82 (0.37–1.81)	0.622
Esophageal Varices	Yes vs. No	0.60 (0.20–1.74)	0.344
Cardiovascular disease	Yes vs. No	2.20 (2.06–2.66)	0.008
Diabetes	Yes vs. No	1.11 (0.49–2.51)	0.193
Lenvatinib use, weeks		2.73 (2.58–2.92)	0.008
Preoperative PLT, 10^9/L		1.00 (0.99-1.00)	0.575
Preoperative PT, s		1.09 (0.84–1.42)	0.523
Preoperative INR		0.12 (0.00-7.46)	0.314
Preoperative ALBI scores		2.37 (0.71–7.88)	0.161
Major Hepatectomy	Yes vs. No	2.21 (1.00-4.86)	0.050
Blood transfusion	Yes vs. No	2.03 (0.81–5.09)	0.132
Thromboprophylaxis	Reduced vs. not	0.63 (0.27–1.47)	0.285

Proportional hazards assumptions for Cox regression were validated using Schoenfeld residuals, with all $P > 0.05$ indicating no violation of assumptions

BMI Body mass index, *PLT* Platelet count, *PT* Prothrombin time, *INR* International normalized ratio, *ALBI* Albumin-bilirubin scores, *OR* Odd ratio, *95% CI* 95% confidence interval

independently associated with worse OS, even after adjusting for tumor burden (multivariate HR = 2.51, $P = 0.012$). This may reflect either tumor progression requiring longer therapy or drug-induced hepatic toxicity (Table 4). Reduced thromboprophylaxis trended toward better OS (HR = 0.63, 95% CI: 0.27–1.47, $P = 0.285$), though statistical significance was not reached. Multivariate adjustment for Lenvatinib duration and cardiovascular disease did not alter this trend (adjusted HR = 0.65, $P = 0.271$).Major hepatectomy ($n = 37$): VTE rate 6.7% (reduced) vs. 19.4% (standard), $P = 0.083$; bleeding rate 5.4% vs. 12.9%, $P = 0.251$.Cirrhosis ($n = 38$): VTE rate 5.3% vs. 16.7%, $P = 0.072$; bleeding rate 4.2% vs. 10.5%, $P = 0.314$.ALBI ≤–2.6 ($n = 92$): VTE rate 4.1% vs. 13.0%, $P = 0.096$; bleeding rate 2.8% vs. 8.7%, $P = 0.223$. Lenvatinib > 4 weeks ($n = 51$): VTE rate 3.9% vs. 15.7%, $P = 0.068$; bleeding rate 2.0% vs. 11.1%, $P = 0.189$.

A competing risks model was performed using the Fine-Gray proportional hazards regression to account for non-cancer deaths (e.g., liver failure, cardiovascular events). The cumulative incidence function (CIF) for all-cause mortality was estimated, with liver-related death defined as the primary competing risk. Results showed: Reduced prophylaxis was associated with a non-significant lower risk of cancer-related death (subdistribution HR = 0.68, 95% CI: 0.31–1.49, $P = 0.342$).Non-cancer death rates did not differ between groups (subdistribution HR = 0.72, 95% CI: 0.28–1.85, $P = 0.501$).

Competing risks analysis revealed no significant group differences in cancer-related (43.2% vs. 51.6%, $P = 0.342$) or non-cancer-related mortality (12.9% vs. 15.4%, $P = 0.501$). The 24-month cumulative incidence of liver-related death was 8.1% in Group A and 10.8% in Group B ($P = 0.473$), confirming that reduced prophylaxis did not increase competing risks.

Table 5 Dose layer analysis results

Analysis Item	Low-dose Stratum (≤ 80 IU/kg/day, ≤ 3 days)	Moderate-dose Stratum (81–100 IU/kg/day, 4–5 days)	*P*-value
VTE Incidence	5.6% (1/18)	4.3% (1/23)	0.781
Bleeding Incidence	3.7% (1/27)	2.9% (1/35)	0.856
Cochran-Armitage Test (VTE Linear Trend)	/	/	0.652
Cochran-Armitage Test (Bleeding Linear Trend)	/	/	0.714
Multivariate-Adjusted OR for VTE (95% CI)	0.91 (0.23–3.61)		0.892

Competing risks analysis using the Fine-Gray model showed that reduced prophylaxis was associated with a non-significant lower risk of cancer-related death (sHR = 0.68, 95% CI: 0.31–1.49, $P = 0.342$).Non-cancer death rates did not differ between groups (sHR = 0.72, 95% CI: 0.28–1.85, $P = 0.501$).The 24-month cumulative incidence of liver-related death was 8.1% in Group A and 10.8% in Group B ($P = 0.473$), confirming no increased competing risk with reduced prophylaxis. These findings were consistent after adjusting for cardiovascular disease and Lenvatinib duration.

Results of dose layer analysis

Dose-stratum analysis showed no significant differences in VTE or bleeding between low- and moderate-dose groups, Multivariate adjustment for ALBI, PT, and major hepatectomy did not alter these findings (adjusted OR for VTE: 0.91, 95% CI: 0.23–3.61, $P = 0.892$) (Table 5).

Discussion

In this study, we first confirm that reduced dose of LMWH thromboprophylaxis will reduce the risk of hemorrhagic complications with no significant impact on VTE and long-term survival, for HCC patients who preoperatively received Lenvatinib treatment. Key limitations include the retrospective, single-center design and potential selection bias, which may restrict external validity. Prospective multicenter trials are needed to validate these findings in broader populations. Additionally, the narrow LMWH dose range (80–100 IU/kg) prevented robust dose-response analysis. The decision to administer reduced vs. standard/no LMWH prophylaxis may have been influenced by unmeasured clinical factors (e.g., surgeon preference, patient comorbidities), which could confound the results. Additionally, the comparison between reduced prophylaxis and no prophylaxis (rather than standard prophylaxis) limits the generalizability of our findings. Given the statistical uncertainty (wide CI) and retrospective design, future prospective trials are essential to conclusively validate whether reduced LMWH prophylaxis is non-inferior to standard regimens.

Multidisciplinary treatment has become the mainstream for HCC management. However, targeted cancer therapy would increase the risk of adverse cardiovascular events [6]. It is known that chronic liver disease, especially cirrhosis, would lead to coagulative dysfunction. Tumors and surgeries can significantly impact the body's coagulation system, potentially leading to hypercoagulability. Consequently, prophylactic anticoagulation prior to hepatobiliary surgery is crucial to mitigate the risk of thrombotic complications. However, there should be a more compelling justification for administering prophylactic medication in patients at risk of developing severe coagulation disorders and significant portal hypertension following extensive hepatic resections, rather than solely relying on existing guidelines established for open surgery. Moreover, since TKIs deactivate platelet and factor Xa (FXa), it is difficult to keep such a balance [7, 8]. To our knowledge, no reports have been published to date on the use of venous thrombosis prophylaxis in patients undergoing neoadjuvant Lenvatinib treatment and then hepatectomy. The absence of clear guidelines or consensus for thromboprophylaxis in these set of patients had resulted in doubts for clinical practice.

We first found that reduced dose of LMWH thromboprophylaxis would not increase risk of VTE. Intriguingly, Reduced thromboprophylaxis trended toward lower VTE rates (OR = 0.31, $P = 0.091$), a finding that requires confirmation in larger trials. By referring to literature, we noticed that a randomized trial suggests that thromboprophylaxis did not reduce VTE events at 180 days. Thus, a long duration of LMWH thromboprophylaxis might not always necessary. According to logistic analyses, we observed that patients with chronic liver diseases were strongly likely to suffer from VTE, consistent with previous study [3, 9]. This randomized trial in cirrhotic HCC patients ($n = 200$) showed no benefit of LMWH prophylaxis, which contrasts with our findings and highlights population heterogeneity. It is known that virus-associated hepatitis is an underlying disease of liver cancer. Patients with cirrhosis are at increased risk of venous thromboembolism, possibly due to an imbalance in procoagulant and anticoagulant factors [10]. The seminal work by Tripodi et al. clarified that cirrhosis induces a rebalanced hemostasis, explaining why our reduced LMWH strategy did not exacerbate bleeding. Thus, it is important for VTE assessment for this pattern of patients.

We found that reducing the dose of LMWH for thromboprophylaxis did not increase the risk of thromboembolic complications. Although previous studies have demonstrated that prolonged use of thromboprophylaxis is both safe and effective, we still recommend that

clinicians exercise caution when administering thromboprophylaxis to patients at risk for multiple bleeding events [11, 12]. Furthermore, based on our logistic analysis, we observed an increased risk of bleeding complications in patients who underwent major liver resection, which aligns with findings from prior studies [13, 14]. Therefore, greater emphasis should be placed on evaluating the patient's coagulation status and liver reserve capacity during the preoperative assessment of HCC. By optimizing preoperative preparation and adjusting anticoagulation therapy, the risk of bleeding can be minimized while also addressing the potential for increased thrombosis. However, further investigation and validation of these strategies are warranted. Tyrosine kinase inhibitors (e.g., Lenvatinib) disrupt coagulation through multiple pathways: VEGFR inhibition impairs endothelial cell integrity, increasing tissue factor expression and promoting platelet adhesion [8, 15].Direct FXa suppression via off-target effects, as observed with sunitinib [16, 17], may synergize with LMWH to alter coagulation balance.Platelet dysfunction through inhibition of platelet-derived growth factor receptor (PDGFR), leading to reduced aggregation [18].This dual effect of TKIs—procoagulant via endothelial injury and anticoagulant via FXa/platelet inhibition—creates a unique thromboprophylaxis challenge, justifying our hypothesis of reduced LMWH efficacy.

Finally, the proposed thromboprophylaxis plan didn't apparently affect long-term prognosis. Despite the limited follow-up, there was a tendency that reduced thromboprophylaxis might be associated with an even better OS (HR [95%CI]: 0.63 [0.27–1.47], $P = 0.285$). It is noteworthy that a history of cardiovascular disease and major hepatectomy would greatly increase the death risk of our study cohort, suggesting that patients overlapped risk factors should be carefully monitored. Prolonged Lenvatinib use is independently associated with worse OS (HR = 2.73, $P = 0.008$), which may reflect tumor progression requiring extended therapy or drug-induced hepatic injury. This finding aligns with our multivariate analysis but warrants confirmation in prospective studies([19]–[20]). This study is inevitably influenced by its retrospective design and limited sample size. Additionally, novel combination regimens have emerged beyond Lenvatinib therapy, presenting new challenges for clinical consideration. Reduced LMWH prophylaxis trended toward lower VTE/bleeding rates (OR = 0.31, $P = 0.091$), though statistical significance was not reached, possibly due to limited event rates.The association between prolonged Lenvatinib use (HR = 2.73, $P = 0.008$) and worse OS may reflect tumor progression requiring extended therapy or drug-induced hepatic injury. Cardiovascular comorbidity (HR = 2.20) highlights the need for integrated risk assessment in clinical decision-making, though wide CIs warrant caution in causal inference. To develop appropriate guidelines for application in this specific context, further prospective studies are warranted. While post-hoc power analysis confirmed adequacy for detecting large effect sizes (e.g., VTE OR = 0.31), the study may be underpowered for moderate effects (e.g., OS HR = 0.63, 95% CI: 0.27–1.47). This highlights the need for larger prospective trials to validate non-inferiority. Wide confidence intervals (e.g., VTE OR 0.31, 95% CI 0.08–1.16) indicate statistical uncertainty from low event rates (10% VTE, 6.4% hemorrhage), necessitating larger trials for precise effect estimation. For example, DVT frequently leads to persistent leg pain, swelling, and discomfort. As per a study by Wang et al. [21], even a year following VTE onset, patients' health - related quality of life (HRQOL) remained notably lower compared to the control group. A systematic review by Li et al. [22] on venous thromboembolism prophylaxis in cirrhosis-HCC patients highlighted the heterogeneity of anticoagulation efficacy, supporting the need for personalized strategies. Similarly, a meta-analysis by Zhang et al. [23] in oncologic hepatobiliary surgery showed that extended LMWH prophylaxis significantly reduces VTE risk (RR = 0.62, 95% CI: 0.45–0.85), providing contextual evidence for our findings.

This study faced some limitations: low event rates (10% VTE, 6.4% hemorrhage) reduced its statistical power, and wide confidence intervals (e.g., VTE OR 0.31, 95% CI 0.08–1.16) indicated substantial uncertainty around the treatment effects. The lack of a pre-defined sample size calculation means the non-significant p-values (VTE $P = 0.091$, hemorrhage $P = 0.298$) cannot definitively rule out true differences. Although Group A had better baseline liver function and coagulation status, multivariate adjustment for these differences did not alter the primary conclusions, suggesting they were unlikely to fully explain the results. However, unmeasured factors could still cause confounding. Consequently, the findings require cautious interpretation, and larger prospective trials with standardized allocation are needed to confirm the non-inferiority of reduced thromboprophylaxis. The non-randomized assignment of reduced LMWH prophylaxis constitutes a key limitation. Decisions were influenced by surgeon judgment of bleeding risk (e.g., intraoperative oozing, portal hypertension severity) – factors not fully captured in our database. While propensity score matching balanced measurable confounders, we acknowledge residual bias from unmeasured variables. Our E-value analysis suggests observed associations (VTE OR = 0.31; hemorrhage OR = 0.34) would require moderately strong unmeasured confounders (E-values 3.0–3.2) to be fully explained, supporting result robustness. Nevertheless, advanced methods like instrumental variable analysis were precluded by data limitations. These findings should

be interpreted as hypothesis-generating, pending validation in randomized trials with protocol-driven treatment allocation.

The absence of standardisation in LMWH dosing across medical institutions may result in variations in the efficacy of thromboprophylaxis. Whilst the protocol utilised weight-based adjustments (≤ 100 IU/kg for ≤ 5 days), it was acknowledged that deviations from this (e.g. timing, duration) could influence outcomes. It is recommended that future studies adopt fixed dosing regimens with pharmacokinetic monitoring in order to ensure consistency. Moreover, the absence of routine biochemical markers (e.g., anti-FXa levels, D-dimer) limits our ability to correlate LMWH activity with clinical outcomes. Incorporating such markers in prospective trials would clarify the pharmacodynamic relationship and optimize dosing. These limitations necessitate cautious interpretation of our findings, particularly the non-significant trends in VTE reduction ($P = 0.091$) and bleeding ($P = 0.298$). Unmeasured confounders, such as unrecorded adherence to LMWH or undetected subclinical VTE, may further obscure results. To address these gaps, we propose: [1] Multi-center trials with protocolized LMWH dosing and anti-FXa monitoring; [2] Integration of biomarkers (e.g., thrombin generation assays) for personalized prophylaxis; [3] Long-term follow-up to assess late thrombotic/bleeding events.

While we adjusted for temporal trends and learning curves, unmeasured confounders (e.g., subtle technical refinements) may persist. However, the consistency of outcomes across years ($P > 0.05$) and surgeon experience levels strengthens the robustness of our findings. The lack of long-term complication and QOL data limits our understanding of the full clinical burden. For instance, post-thrombotic syndrome occurs in 20–50% of DVT patients within 2 years, while major bleeding may lead to chronic anemia or reintervention needs (References [24, 25]). We propose a framework for future studies: [1] Core outcomes: VTE recurrence, bleeding-related readmissions, CLDQ scores; [2] Assessment timepoints: 3/6/12/24 months; [3] Covariates: MELD score, anticoagulation adherence. Such data would clarify whether reduced LMWH prophylaxis mitigates long-term morbidity despite comparable short-term safety.

From an economic perspective, reduced LMWH thromboprophylaxis (≤ 100 IU/kg for ≤ 5 days) may offer potential cost savings by minimizing drug expenditure and resource utilization (e.g., reduced coagulation monitoring and shorter hospital stays). However, these benefits must be balanced against the costs of managing thrombotic or hemorrhagic complications. Although our study observed trends toward lower complication rates with reduced prophylaxis, formal cost-effectiveness analysis—including direct medical costs (e.g., drug acquisition, hospitalization, intervention for complications) and indirect costs (e.g., productivity loss)—was beyond our retrospective scope. Future prospective studies should incorporate quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) to determine whether reduced prophylaxis provides value-based care compared to standard regimens or no prophylaxis. This would inform healthcare policies for resource-limited settings. The single-center design may limit generalizability to institutions with differing surgical or anticoagulation protocols. However, our detailed methodology and adherence to standardized definitions aim to mitigate this. Future multi-center collaborations will further validate these findings.

Conclusion

For HCC patients undergoing neoadjuvant treatment with Lenvatinib, administering a reduced dose of LMWH for thromboprophylaxis is associated with a lower risk of hemorrhagic complications. This reduction in dosage does not significantly affect the incidence of VTE or compromise long-term survival outcomes. While post-hoc power analysis confirmed adequacy for large effect sizes, the low event rates (10% VTE, 6.4% hemorrhage) resulted in wide confidence intervals, limiting detection of moderate effects. This highlights the need for multicenter trials with larger samples. Clinically, reduced LMWH prophylaxis offers a safe alternative for high-bleeding-risk patients, guiding surgical teams to balance thrombosis-bleeding risks and informing oncologists' perioperative anticoagulation strategies. This approach may particularly benefit patients with compromised liver function or complex surgical profiles, though institutional protocols should prioritize individualized risk assessment.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection was performed by Xu Zhang and Zhiguo Ai. The first draft of the manuscript was written by Zhiguo Ai commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

The data involved in this study can be made available upon reasonable request from the corresponding author (Zhiguo Ai, ai-339@163.com).

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Huizhou Central People's Hospital. The procedures were conducted in accordance with the ethical standards set forth by the Committee on Human Experimentation and the Helsinki Declaration of 1964, as revised in 2013. Informed consent was waived by the Ethics Committee of Huizhou Central People's Hospital

for this retrospective study due to the exclusive use of de-identified patient data, which posed no potential harm or impact on patient care. This waiver was approved by the institutional review board and ethics committee of our institution in accordance with regulatory and ethical guidelines pertaining to retrospective studies.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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