J Chin Med Assoc

ORIGINAL ARTICLE

A predictive model incorporating inflammation markers for high-grade surgical complications following liver resection for hepatocellular carcinoma

Hsiang-Ling Wu[a,b], Hsin-Yi Liu[c,d], Wan-Chi Liu[c,d], Ming-Chih Hou[b,e], Ying-Hsuan Tai[c,d,*]

[a]Department of Anesthesiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Department of Anesthesiology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, ROC; [d]Department of Anesthesiology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC; [e]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

Background: Systemic inflammation and immune deficiency predispose surgical patients to infection and adversely affect postoperative recovery. We aimed to evaluate the prognostic ability of inflammation and immune-nutritional markers and to develop a predictive model for high-grade complications after resection of hepatocellular carcinoma (HCC).

Methods: This study enrolled 1431 patients undergoing liver resection for primary HCC at a medical center. Preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, prognostic nutritional index, Model for End-Stage Liver Disease score, Albumin-Bilirubin score, Fibrosis-4 score, and Aspartate Aminotransferase to Platelet Ratio Index score were assessed. Stepwise backward variable elimination was conducted to determine the factors associated with Clavien-Dindo grade III to V complications within 30-day postoperative period. The predictive model was internally validated for discrimination performance using area under the receiver operating characteristic curve (AUC).

Results: A total of 106 (7.4%) patients developed high-grade complications. Four factors independently predicted a high-grade postoperative complication and were integrated into the predictive model, including NLR (adjusted odds ratio: 1.10, 95% confidence interval [CI], 1.02-1.19), diabetes mellitus, extent of hepatectomy, and intraoperative blood loss. The AUC of the model was 0.755 (95% CI, 0.678-0.832) in the validation dataset. Using the cutoff value based on Youden's index, the sensitivity and specificity of the risk score were 59.0% and 76.3%, respectively.

Conclusion: Preoperative NLR independently predicted a high-grade complication after resection of HCC. The predictive model allows for identification of high-risk patients and appropriate modifications of perioperative care to improve postoperative outcomes.

Keywords: Clavien-Dindo classification; Hepatectomy; Neutrophil-to-lymphocyte ratio; Surgical outcome

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide, leading to approximately 830,000 deaths in 2020.[1] Despite recent advancements in targeted molecular therapy, surgical resection of the primary tumor remains the gold standard treatment for resectable HCC.[2] However, liver resection carries a risk of postoperative complications for patients with reduced liver functional reserve, with a reported rate of up to 47.7%.[3] Notably, postoperative complications may increase the risk of long-term mortality and recurrence following liver resection for HCC.[4]

Host immunity is important for cancer patients to protect against surgical stress and related complications. Preoperative immune dysfunction is known to increase the risk of mortality and morbidity after major surgery.[5] Surgical trauma suppresses immune function and triggers systemic inflammation, which may adversely impact the prognosis of cancer patients.[6] In addition, malnutrition is associated with impaired immune function and wound healing, predisposing patients to adverse postoperative outcomes.[7] Mounting evidence indicates that inflammation and immune-nutritional markers may predict complications after surgical resection of miscellaneous cancers, including lung cancer,[8] colorectal cancer,[9] gastric cancer,[10] and bladder cancer.[11] However, few studies have investigated the prognostic role of inflammation and immune-nutritional markers for postoperative complications in HCC.[12–15] Importantly, there have been several

*Address correspondence. Dr. Ying-Hsuan Tai, Department of Anesthesiology, Shuang Ho Hospital, Taipei Medical University, 291, Zhongzheng Road, Zhonghe District, New Taipei City 235, Taiwan, ROC. E-mail address: 18045@s.tmu.edu.tw (Y.-H. Tai).

Conflicts of interest: Dr. Ming-Chih Hou, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 845-852.

Received August 25, 2021; accepted November 5, 2021.

doi: 10.1097/JCMA.0000000000000713.

research flaws in previous studies, including small sample sizes (<1000 patients),[12–14] insufficient adjustment for confounders,[12] and no comparison of the different markers.[12–15] Furthermore, the results of previous studies were not validated,[12–15] and to the best of our knowledge, there is still no predictive model based on inflammation or immune-nutritional indices for postoperative complications pertinent to HCC in the current literature.

We conducted a single-center cohort study to evaluate the prognostic role of inflammation and immune-nutritional markers for high-grade postoperative complications after liver resection for HCC. There were two objectives in this study. First, we sought to compare various representative preoperative noninvasive serum markers and their potential predictive ability for postoperative complications, including the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the prognostic nutritional index (PNI), the Model for End-Stage Liver Disease (MELD) score, the Albumin-Bilirubin score, the Fibrosis-4 score, and the Aspartate Aminotransferase to Platelet Ratio Index (APRI) score. Second, we aimed to integrate these markers with other clinical factors to build a predictive model for severe complications following resection of HCC.

2. METHODS

2.1. Patient selection and clinical setting

The present study was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB-TPEVGH No. 2021-07-035BC). The need for written informed consent was waived by the Institutional Review Board due to the study's retrospective nature, and the study was conducted in accordance with all current guidelines and regulations.

We included a total of 2215 consecutive patients who underwent liver resection at the medical center from January 2005 to December 2016. Patients were excluded for the following reasons: repeat operation, liver transplantation, pathology-proven benign tumors, metastatic liver cancer, non-HCC cancer, HCC with lymph node or distant metastasis, Child-Pugh class C, Barcelona Clinic Liver Cancer (BCLC) stage C or D, and critical missing data. A total of 1431 patients were selected for analysis (Fig. 1).

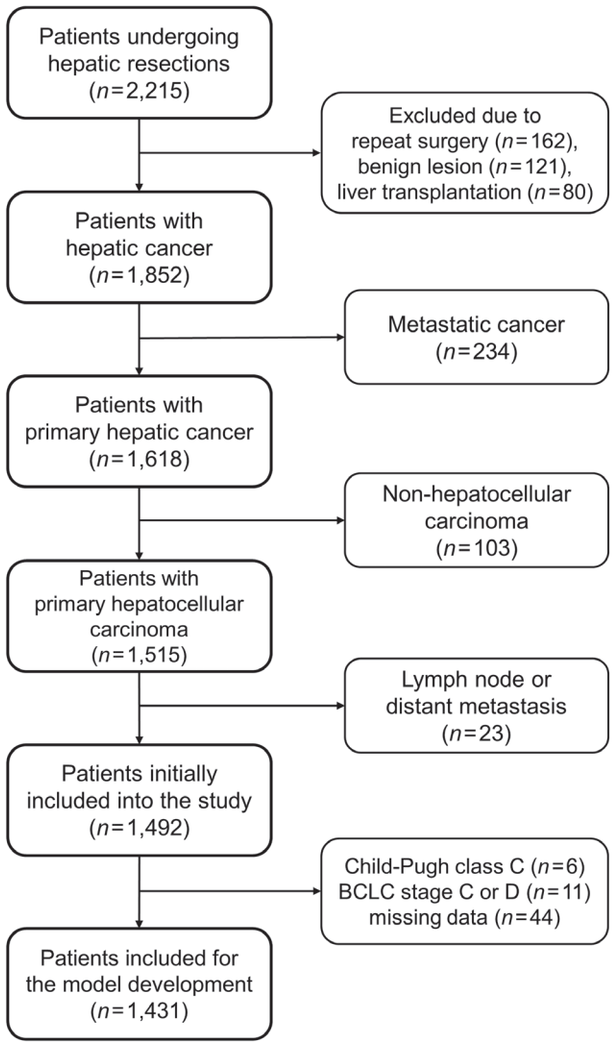

Fig. 1 Flow diagram for patient selection.

2.2. Noninvasive serum markers for assessment

The NLR was calculated by neutrophil count/ lymphocyte count. In the same way, the PLR was equal to the platelet count/ lymphocyte count. PNI was equal to 10 × serum albumin ($g \cdot dL^{-1}$) + 0.005 × lymphocyte count ($10^3 \cdot \mu L^{-1}$).[16] The MELD score was equal to 3.78 × ln (total bilirubin [$mg \cdot dL^{-1}$]) + 11.2 × ln (international normalized ratio) + 9.57 × ln (serum creatinine [$mg \cdot dL^{-1}$]) + 6.43.[17] The Albumin-Bilirubin score was equal to $\log_{10}$ (total bilirubin [$\mu mol \cdot L^{-1}$] × 0.66) + [serum albumin [$g \cdot L^{-1}$] × -0.0852].[18] The Fibrosis-4 score was equal to age (years) × aspartate aminotransferase (AST) ($U \cdot L^{-1}$)/(platelet count [$10^3 \cdot \mu L^{-1}$] × alanine aminotransferase [ALT]$^{1/2}$ [$U \cdot L^{-1}$]).[19] The APRI score was equal to [AST level/AST (upper limit of normal range)] × 100/platelet count ($10^3 \cdot \mu L^{-1}$).[20] The concentrations of serum albumin, creatinine, total bilirubin, AST, ALT, neutrophils, lymphocytes, and platelets in the peripheral blood 1 day before the surgery, were retrospectively collected.

2.3. Liver resection

At the medical center, all liver resections were performed by an experienced general surgeon who performed at least 50 cases annually. The liver parenchyma was transected using a clamp-crush technique. Intermittent Pringle's maneuver and argon beam coagulator were routinely used to control hemorrhage. For selected patients, minimally invasive surgery using a laparoscopic or robotic technique was performed from July 2011.

2.4. Postoperative complications

The primary outcome of the current study was high-grade postoperative complications which occurred within 30 days after the surgery. A high-grade complication was defined as grade III or higher using the Clavien-Dindo (CD) classification system, a representative ranking system for postoperative complications used worldwide.[21] We evaluated CD grades III to V (III: requiring surgical, endoscopic, or radiological intervention; IV: requiring intensive care management; V: death of a patient) because such complications require invasive treatment.[21,22]

2.5. Variables considered for analysis

For prediction modeling, we selected preoperative and intraoperative factors potentially associated with postoperative complications based on the available data, physiological plausibility and the existing literature. In addition to demographics and coexisting diseases, clinical characteristics were reviewed, including Child-Pugh class, clinically significant portal hypertension (hepatic venous pressure gradient ≥10 mm Hg), presence of esophageal varices, hepatitis viral serology, prior receipts of antiviral therapy for hepatitis B or C, preoperative serum levels of AST, ALT, total bilirubin, gamma-glutamyl transferase, and alpha-fetoprotein.[23–26] Patients were classified according

Table 1

Patient demographics, clinical and pathological characteristics

	Development cohort (n = 835)	Validation cohort (n = 596)	*p*
Age, year	61.6 ± 13.0	60.8 ± 12.5	0.2504
Sex, male	635 (76.1%)	460 (77.2%)	0.6181
Body mass index, kg·m^{-1}	24.4 ± 3.8	24.6 ± 3.6	0.4698
ASA class ≥3	272 (32.6%)	152 (25.5%)	0.0039
Etiology of hepatocellular carcinoma			
Hepatitis B surface antigen positive	567 (67.9%)	389 (65.3%)	0.2966
Hepatitis C antibody positive	180 (21.6%)	135 (22.7%)	0.6224
Alcoholism	63 (7.5%)	40 (6.7%)	0.5476
Child-Pugh class B	24 (2.9%)	23 (3.9%)	0.3028
Clinically significant portal hypertension	81 (9.7%)	61 (10.2%)	0.7389
Esophageal varices	50 (6.0%)	35 (5.9%)	0.9274
Diabetes mellitus	222 (26.6%)	128 (21.5%)	0.0266
Ischemic heart disease	75 (9.0%)	40 (6.7%)	0.1193
Chronic kidney disease	86 (10.3%)	48 (8.1%)	0.1506
Serum markers			
Prognostic nutritional index	48.9 (45.1 to 52.1)	48.9 (45.3 to 52.5)	0.8528
Neutrophil-to-lymphocyte ratio	1.9 (1.4 to 2.8)	1.9 (1.4 to 2.8)	0.5474
Platelet-to-lymphocyte ratio	102.0 (74.4 to 143.6)	100.0 (75.5 to 138.1)	0.4741
MELD score	4.8 (2.5 to 6.8)	4.6 (2.5 to 6.3)	0.0812
Albumin-Bilirubin score	-5.0 (-5.3 to -4.8)	-5.0 (-5.3 to -4.8)	0.7865
Fibrosis-4 score	2.3 (1.5 to 3.6)	2.3 (1.4 to 3.7)	0.7537
APRI score	0.6 (0.4 to 1.0)	0.6 (0.4 to 1.1)	0.5486
Preoperative laboratory tests			
Hemoglobin, g·dL^{-1}	13.3 ± 1.7	13.4 ± 1.7	0.8183
Platelet, 10^3·μL^{-1}	181.5 ± 81.7	178.3 ± 81.2	0.4555
Thrombocytopenia	318 (38.1%)	254 (42.6%)	0.0844
Serum glucose, mg·dL^{-1}	106 ± 39	105 ± 37	0.7987
Serum creatinine, mg·dL^{-1}	1.1 ± 0.8	1.1 ± 0.9	0.9943
International normalized ratio	1.05 ± 0.26	1.04 ± 0.07	0.3604
Total bilirubin ≥ 1.0 mg·dL^{-1}	206 (24.7%)	116 (19.5%)	0.0209
Aspartate aminotransferase > 40 IU·L^{-1}	388 (46.6%)	273 (46.0%)	0.8010
Alanine aminotransferase > 40 IU·L^{-1}	399 (47.8%)	282 (47.3%)	0.8610
Gamma-glutamyl transferase > 50 IU·L^{-1}	352 (44.1%)	238 (42.4%)	0.5317
Alpha-fetoprotein > 20 ng·mL−1	398 (49.0%)	306 (52.7%)	0.1787
Albumin < 3.5 g·dL^{-1}	64 (7.7%)	45 (7.6%)	0.9359
BCLC stage			0.9396
Stage 0	109 (13.1%)	80 (13.4%)	
Stage A	364 (43.6%)	263 (44.1%)	
Stage B	362 (43.4%)	253 (42.5%)	
Pathologic characteristics			
Tumor diameter >5 cm	313 (37.5%)	205 (34.4%)	0.2306
Multifocal cancer	175 (21.0%)	135 (22.7%)	0.4435
Tumor differentiation			0.6983
Good	96 (11.5%)	77 (12.9%)	
Moderate	452 (54.1%)	314 (52.7%)	
Poor or undifferentiated	287 (34.4%)	205 (34.4%)	
Microvascular invasion	564 (67.5%)	416 (69.8%)	0.3656
Extracapsular penetration	359 (43.0%)	243 (40.8%)	0.4012
Inflammation			0.3321
Absent or mild	724 (86.7%)	506 (84.9%)	
Moderate or severe	111 (13.3%)	90 (15.1%)	
Steatosis			0.2969
Absent or mild	790 (94.6%)	556 (93.3%)	
Moderate or severe	45 (5.4%)	40 (6.7%)	
Fibrosis			0.7110
Absent or mild	299 (35.8%)	203 (34.1%)	
Moderate or severe	322 (38.6%)	242 (40.6%)	
Cirrhosis	214 (25.6%)	151 (25.3%)	
Preoperative locoregional therapy	80 (9.6%)	47 (7.9%)	0.2664
Preoperative antiviral therapy	141 (16.9%)	91 (15.3%)	0.4130

Continued next page

Table 1 (Continued)

	Development cohort (n = 835)	Validation cohort (n = 596)	*p*
Surgical and anesthetic management			
Hepatectomy > 2 segments	311 (37.3%)	213 (35.7%)	0.5596
R0 resection	782 (93.7%)	563 (94.5%)	0.5249
Laparoscopic or robotic surgery	54 (6.5%)	36 (6.0%)	0.7430
Epidural anesthesia	321 (38.4%)	227 (38.1%)	0.8914
Intraoperative blood loss (mL)	650 (300 to 1200)	600 (300 to 1250)	0.6920
Blood transfusion	525 (62.9%)	364 (61.1%)	0.4888
Anesthesia time (min)	345 (285 to 435)	335 (270 to 420)	0.0634
Operation period (2011-2016)	432 (51.7%)	320 (53.7%)	0.4654

Values were mean ± SD, count (percent), or median (interquartile range).
APRI = Aspartate Aminotransferase to Platelet Ratio Index; ASA = American Society of Anesthesiologists; BCLC = Barcelona Clinic Liver Cancer; MELD = Model for End-Stage Liver Disease.

to the BCLC staging system.[27] Pathology features comprised tumor size and number, differentiation, microvascular invasion, extracapsular penetration, severity of inflammation, steatosis, and fibrosis.[28,29] Preoperative locoregional therapy consisted of trans-arterial chemoembolization, radiofrequency ablation, and percutaneous ethanol injection. Surgical and anesthetic covariates were extent of hepatectomy (>2 Couinaud liver segments or not), R0 resection, laparoscopic or robotic surgery, epidural anesthesia, intraoperative blood loss and transfusion, and anesthesia time.[22,30–35]

2.6. Statistical analysis

The Shapiro-Wilk test and Kolmogorov-Smirnov test were used to examine the normality of the included variables. Logarithmic transformation was applied to decrease the skewness of non-normal variables. The dataset was randomly partitioned into development and validation datasets in an approximately 60:40 ratio using the RAND function of Statistics Analysis System (SAS), version 9.4 (SAS Institute Inc., Cary, NC). Univariate logistic regression analysis was performed to evaluate the association of noninvasive serum markers and other covariates with high-grade complications in the development dataset. Significant factors in the univariate model were incorporated into the stepwise backward variable elimination procedure to determine independent predictors and to obtain the risk score for postoperative complications, based on minimization of the Akaike's Information Criterion with a *p*-value threshold of 0.05. The validation dataset was used to assess the diagnostic utility of three models, including the initial model (preoperative noninvasive serum markers), more inclusive model (all preoperative predictors), and final model (all preoperative and intraoperative predictors).[36] Model discrimination was estimated using area under the receiver operating characteristic curve (AUC). The optimal cutoff value for risk scores was determined using the joint maximum sensitivity and specificity of the receiver operating characteristic curves associated with complications (Youden's index).[37] We considered $p < 0.05$ to indicate a statistically significant difference for a two-sided test. All the statistical analyses were performed using SAS software.

3. RESULTS

3.1. Patient characteristics

A total of 1431 patients were included in the study and randomly split into the development cohort (n = 835) and the validation cohort (n = 596). Table 1 shows the demographic, clinical and pathological characteristics of the included patients. The distribution of baseline patient characteristics was generally balanced between the two cohorts, except for the American Society of Anesthesiologists class, diabetes mellitus, and level of total bilirubin.

3.2. High-grade postoperative complications

A total of 106 (7.4%) patients developed high-grade complications within 30 days after liver resection, 67 in the development cohort and 39 in the validation cohort. Among them, 72 (5.0%), 21 (1.5%), and 13 (0.9%) had CD grade III, IV, and V complications, respectively. The most common complications were bile leakage (n = 30, 2.1%) in those with CD grade III, and respiratory failure (n = 15, 1.0%) in those with CD grade IV complications (Table 2).

3.3. Factors associated with complications

In the univariate analysis, there were three noninvasive serum markers significantly associated with high-grade complications, including NLR (crude odds ratio [OR]: 1.09, 95% confidence interval [CI], 1.02-1.17), PNI (OR: 0.91, 95% CI,

Table 2

High-grade postoperative complications in the development and validation cohorts

Complication	Development cohort (n = 835)	Validation cohort (n = 596)
Clavien-Dindo grade III[a]		
Bile leakage	15 (1.8%)	15 (2.5%)
Pleural effusion	9 (1.1%)	8 (1.3%)
Wound complication	8 (1.0%)	3 (0.5%)
Intra-abdominal abscess	5 (0.6%)	4 (0.7%)
Massive ascites	3 (0.4%)	0 (0)
Hepatic hemorrhage	2 (0.2%)	2 (0.3%)
Obstructive jaundice	1 (0.1%)	1 (0.2%)
Liver abscess	1 (0.1%)	0 (0)
Pneumothorax	1 (0.1%)	0 (0)
Occlusion of common hepatic duct	1 (0.1%)	0 (0)
Edematous change of bile duct wall	1 (0.1%)	0 (0)
Peritonitis	1 (0.1%)	0 (0)
Duodenal ulcer bleeding	1 (0.1%)	0 (0)
Intestinal obstruction	0 (0)	1 (0.2%)
Acute kidney injury	1 (0.1%)	0 (0)
Clavien-Dindo grade IV		
Respiratory failure	12 (1.4%)	3 (0.5%)
Cerebral infarction	1 (0.1%)	1 (0.2%)
Sepsis	1 (0.1%)	1 (0.2%)
Multiorgan failure	1 (0.1%)	0 (0)
Hepatic failure	0 (0)	0 (0)
Myocardial infarction	1 (0.1%)	0 (0)
Clavien-Dindo grade V		
Death of a patient	8 (1.3%)	5 (0.8%)

[a]Seven and five patients in the development and validation cohorts had two complications.

Table 3

Associations of preoperative and intraoperative factors with high-grade postoperative complications in the development cohort

	Univariate		Multivariable	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Neutrophil-to-lymphocyte ratio	1.09 (1.02-1.17)	0.0147	1.10 (1.02–1.19)	0.0124
Platelet-to-lymphocyte ratio	1.00 (1.00-1.00)	0.1234	.	.
Prognostic nutritional index	0.91 (0.87-0.95)	<0.0001	.	.
MELD score	1.00 (0.94-1.06)	0.8678	.	.
Albumin-Bilirubin score	3.01 (1.67-5.43)	0.0003	.	.
Fibrosis-4 score	1.06 (0.98-1.15)	0.1307	.	.
APRI score	1.12 (0.95-1.32)	0.1720	.	.
Age, year	1.01 (0.99-1.03)	0.2082	.	.
Sex, male	0.85 (0.48-1.49)	0.5605	.	.
Body mass index, kg·m^{-1}	1.03 (0.96-1.10)	0.4482	.	.
ASA class ≥ 3	1.88 (1.14-3.12)	0.0138	.	.
HBsAg positive	0.96 (0.57-1.64)	0.8918	.	.
Anti-HCV Ab positive	0.70 (0.36-1.36)	0.2884	.	.
Alcoholism	2.05 (0.97-4.36)	0.0620	.	.
Child-Pugh class B	1.04 (0.24-4.54)	0.9541	.	.
CSPH	1.09 (0.48-2.48)	0.8295	.	.
Esophageal varices	1.30 (0.50-3.38)	0.5963	.	.
Diabetes mellitus	2.97 (1.79-4.93)	<0.0001	3.08 (1.65-5.78)	0.0004
Ischemic heart disease	1.65 (0.78-3.48)	0.1881	.	.
Chronic kidney disease	1.20 (0.55-2.60)	0.6453	.	.
Hemoglobin, g·dL^{-}1	0.91 (0.79-1.04)	0.1704	.	.
Platelet, 10^{3}·μL^{-1}	1.00 (1.00-1.00)	0.5702	.	.
Thrombocytopenia	1.03 (0.62-1.73)	0.8987	.	.
Serum glucose, mg·dL^{-1}	1.01 (1.00-1.01)	0.0498	.	.
Serum creatinine, mg·dL^{-1}	0.97 (0.70-1.35)	0.8586	.	.
International normalized ratio	1.20 (0.62-2.30)	0.5905	.	.
Total bilirubin ≥ 1.0 mg·dL^{-1}	1.55 (0.91-2.65)	0.1082	.	.
AST > 40 IU·L^{-1}	1.90 (1.14-3.17)	0.0140	.	.
ALT > 40 IU·L^{-1}	1.81 (1.08-3.01)	0.0235	.	.
GGT > 50 IU·L^{-1}	3.13 (1.81-5.41)	<0.0001	.	.
Alpha-fetoprotein > 20 ng·mL^{-1}	1.01 (0.61-1.68)	0.9710	.	.
Albumin < 3.5 g·dL^{-1}	2.32 (1.12-4.80)	0.0232	.	.
BCLC stage		0.1034	.	.
Stage A vs 0	2.10 (0.72-6.15)	0.5292	.	.
Stage B vs 0	2.90 (1.01-8.33)	0.0332	.	.
Tumor diameter > 5 cm	1.14 (0.68-1.89)	0.6200	.	.
Multifocal cancer	2.45 (1.45-4.15)	0.0008	.	.
Tumor differentiation		0.7998	.	.
Moderate vs good	0.86 (0.40-1.85)	0.9599	.	.
Poor or undifferentiated vs good	0.76 (0.34-1.73)	0.5122	.	.
Microvascular invasion	0.85 (0.50-1.43)	0.5398	.	.
Extracapsular penetration	0.54 (0.31-0.93)	0.0253	.	.
Inflammation		0.4330	.	.
Moderate/severe vs absent/mild	1.31 (0.67-2.59)		.	.
Steatosis		0.0621	.	.
Moderate/severe vs absent/mild	2.24 (0.96-5.23)		.	.
Fibrosis		0.1962	.	.
Moderate/severe vs absent/mild	1.24 (0.67-2.30)	0.7870	.	.
Cirrhosis vs absent/mild	1.78 (0.94-3.35)	0.0860	.	.
Preoperative locoregional therapy	1.52 (0.72-3.20)	0.2672	.	.
Preoperative antiviral therapy	1.08 (0.56-2.08)	0.8155	.	.
Hepatectomy > 2 segments	2.38 (1.43-3.94)	0.0008	2.23 (1.18-4.22)	0.0137
R0 resection	0.66 (0.27-1.61)	0.3644	.	.
Laparoscopic or robotic surgery	0.42 (0.10-1.78)	0.2409	.	.
Epidural anesthesia	0.95 (0.57-1.59)	0.8429	.	.
Intraoperative blood loss (mL)[a]	1.82 (1.49-2.24)	<0.0001	1.73 (1.38-2.16)	<0.0001
Blood transfusion	4.78 (2.25-10.14)	<0.0001	.	.
Anesthesia time, min[a]	3.53 (2.00-6.23)	<0.0001	.	.
Operation period (2011-2016 vs 2005-2010)	1.75 (1.04-2.93)	0.0354	.	.

ALT = alanine aminotransferase; Anti-HCV Ab = hepatitis C antibody; ASA = American Society of Anesthesiologists; APRI = Aspartate Aminotransferase to Platelet Ratio Index; AST = aspartate aminotransferase; BCLC = Barcelona Clinic Liver Cancer; CI = confidence interval; CSPH = clinically significant portal hypertension; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; MELD = Model for End-Stage Liver Disease; OR = odds ratio.

[a]On base-2 logarithmic scale.

0.87-0.95), and Albumin-Bilirubin score (OR: 3.01, 95% CI, 1.67-5.43). Other significant factors were American Society of Anesthesiologists class, diabetes mellitus, serum levels of glucose, AST, ALT, gamma-glutamyl transferase, and albumin, multifocal cancer, extent of hepatectomy, intraoperative blood loss, blood transfusion, anesthesia time, extracapsular penetration, and operation period (Table 3).

The stepwise backward variable elimination procedure determined four independent predictors for postoperative complications, including NLR (adjusted OR: 1.10, 95% CI, 1.02-1.19), diabetes mellitus (adjusted OR: 3.08, 95% CI, 1.65-5.78), hepatectomy >2 segments (adjusted OR: 2.23, 95% CI, 1.18-4.22), and intraoperative blood loss (adjusted OR: 1.73, 95% CI, 1.38-2.16, on base-2 logarithm) (Table 3).

Combining these four factors, the estimated risk score can be calculated using the following formula: risk score = 0.0957 × NLR + 1.1264 × (diabetes mellitus or not) + 0.8017 × (hepatectomy > 2 segments or not) + 0.5458 × $\log_2$ (intraoperative blood loss in milliliter) – 8.9299 (constant).

According to the estimated risk score, the probability of developing high-grade complications can be obtained as follows: probability = (exp [risk score]/(1+ exp [{risk score}]) × 100%.[38]

3.4. Diagnostic utility of predictive models

The AUCs for the predictive models were 0.568 (95% CI, 0.476-0.660) for the initial model, 0.638 (95% CI, 0.542-0.733) for the more inclusive model, and 0.755 (95% CI, 0.678-0.832) for the final model (Table 4 and Fig. 2). The diagnostic utility of the final model was greater for hepatitis C-related HCC (AUC: 0.875, 95% CI, 0.779-0.972) and non-hepatitis B or C HCC (AUC: 0.893, 95% CI, 0.813-0.974) compared with hepatitis B-related HCC. Based on Youden's index of the AUC, the optimal cutoff for the risk score for postoperative complications was determined as –2.5103 with a sensitivity of 59.0% and a specificity of 76.3%.

4. DISCUSSION

This study showed that preoperative NLR acts as a predictor for high-grade complications after surgical resection of HCC. Additionally, a predictive model incorporating NLR and other easily obtained clinical factors was developed for risk stratification of complications. Our study has several strengths for investigating the prognostic role of inflammation and immune-nutritional markers for postoperative complications. First, we included a relatively large patient sample to increase the statistical power needed to detect a putative association between markers while adjusting for a comprehensive list of covariates and conducting model validations. Second, we compared different noninvasive serum markers and thereby created a predictive model, which was lacking in previous studies.[12–15] Our results provide an important implication for risk stratification and perioperative management in liver resections for HCC.

Our analyses showed that patients with higher preoperative NLR had a higher risk of high-grade complications after hepatectomy for HCC, in line with two previous studies.[39,40] Our results also suggested that neither preoperative PLR nor PNI were associated with postoperative complications after liver resection, contrasting with some previous studies.[12–15] Discrepancies in the type and severity of complications, treatment modalities, and disease characteristics may explain the inconsistent findings across studies. In the present study, we proposed a validated predictive model, which considered a variety of covariates. Validating a predictive model is essential to ensure that it can accurately predict the outcome of interest.[36] However, previous works failed to validate their models,[12–15] and it is unclear whether their results can be generalized to other datasets with similar predictive ability.

Our results indicated that preoperative NLR was an important predictor for severe postoperative complications after liver resection. In addition, the variable selection analysis demonstrated that the significance of NLR for predicting complications surpassed some conventional factors, including Child-Pugh class and baseline liver function. NLR in the peripheral blood reflects the balance between systemic inflammation and immune function and is recognized as a prognostic index for a variety of diseases.[41] Over the past two decades, there is accumulating evidence supporting the theory that perioperative NLR can predict long-term survival and recurrence after cancer treatment.[42–44] There are some possible mechanisms to explain the association between preoperative NLR and postoperative complications after liver resection. First, neutrophils may facilitate tumor spreading via the production of reactive oxygen species, the release of circulating vascular endothelial growth factor, and overexpression of pro-metastasis protease.[45,46] Second, lymphocytes exert an anti-cancer effect by inducing cytotoxic cell death and producing cytokines that suppress tumor proliferation and metastatic ability.[47] Accordingly, elevated NLR before surgery suggests increased neutrophil counts and/or decreased lymphocyte counts, which are linked to a compromised immune response to residual cancer cells after surgical resection. Third, a decreased lymphocyte count itself reflects an immunosuppressive state and a vulnerability to infections. A previous study has shown that perioperative lymphocytopenia independently predicts postoperative pneumonia after surgical resection of lung cancer.[48]

Table 4

Diagnostic utility of the models for predicting high-grade postoperative complications in the validation cohort

	Initial model (NLR)		More inclusive model (NLR + DM)		Final model (NLR + DM + EH + BL)	
	AUC (95% CI)	*p*	AUC (95% CI)	*p*	AUC (95% CI)	*p*
All	0.568 (0.476-0.660)	0.1496	0.638 (0.542-0.733)	0.0049	0.755 (0.678-0.832)	<0.0001
Hepatitis B-related	0.535 (0.406-0.664)	0.5953	0.616 (0.472-0.761)	0.1150	0.736 (0.619-0.852)	<0.0001
Hepatitis C-related	0.662 (0.511-0.813)	0.0357	0.753 (0.641-0.865)	<0.0001	0.875 (0.779-0.972)	<0.0001
Non-hepatitis B or C	0.521 (0.343-0.699)	0.8163	0.607 (0.397-0.816)	0.3182	0.893 (0.813-0.974)	<0.0001
BCLC stage 0	0.716 (0.478-0.955)	0.0759	0.744 (0.542-0.946)	0.0179	0.797 (0.482-1.000)	0.0643
BCLC stage A	0.595 (0.431-0.760)	0.2573	0.664 (0.495-0.833)	0.0579	0.722 (0.571-0.873)	0.0039
BCLC stage B	0.563 (0.444-0.682)	0.3029	0.657 (0.522-0.792)	0.0223	0.767 (0.678-0.856)	<0.0001
Hepatectomy ≤ 2 segments	0.609 (0.489-0.730)	0.0762	0.688 (0.574-0.801)	0.0012	0.782 (0.689-0.876)	<0.0001
Hepatectomy > 2 segments	0.560 (0.426-0.693)	0.3813	0.590 (0.441-0.738)	0.2388	0.746 (0.641-0.852)	<0.0001

AUC = area under receiver operating characteristic curve; BCLC = Barcelona Clinic Liver Cancer; BL = intraoperative blood loss; CI = confidence interval; DM = diabetes mellitus; EH = extent of hepatectomy (>2 segments or not); NLR = neutrophil-to-lymphocyte ratio.

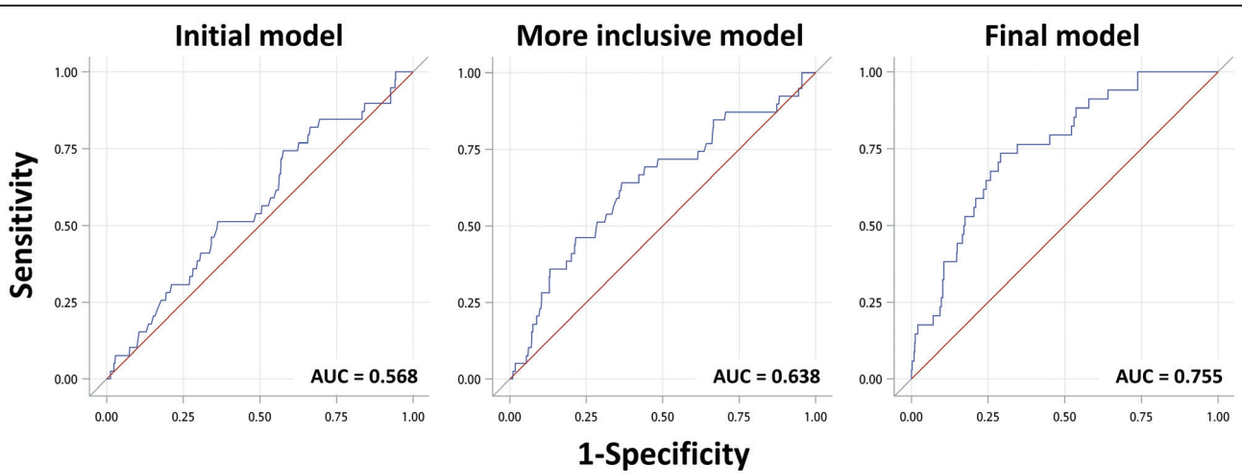

Fig. 2 Receiver operating characteristic curves of the predictive models for high-grade postoperative complications in the validation dataset.

Our model showed that a combination of preoperative and intraoperative factors better predicted the occurrence of critical complications after liver resection. First, we found that coexisting diabetes mellitus acted as a risk factor for complications. Accordingly, blood glucose should be closely monitored and controlled during the perioperative period.[49] Second, given that intraoperative blood loss and perioperative blood transfusion were linked to greater mortality rates after cancer surgery, strategies aimed at reducing blood loss and the use of blood transfusion during liver resection should be further developed, especially in cirrhotic liver.[33–35,50] Third, high-risk patients may need close observation and intensive care for possible bile leakage, infection, and organ failure after surgery. More studies are required to validate the efficacy of our model in reducing complications after liver resection.

There were some limitations to this study. First, our datasets did not include C-reactive protein (CRP), which was not a routine test for patients undergoing liver resection at the center. Therefore, we could not analyze and compare the predictive ability of CRP-related prognostic parameters.[51] Second, low-grade complications were not included. Consequently, our results were not applicable to these outcomes. Third, the predictive accuracy of our model was modest. Additional studies are needed to explore other novel factors which could predict complications with better accuracy. Fourth, the proposed model needs further validation using datasets with different patient characteristics (e.g., viral serology and type of neoplasm) and clinical settings before it can be used in clinical practice.[52]

In conclusion, preoperative NLR independently predicted a high-grade complication after liver resection for HCC. After integrating NLR with diabetes mellitus, extent of liver resection, and intraoperative blood loss, the predictive model demonstrated moderate diagnostic accuracy for postoperative complications. The model will have clinical utility for risk stratification and the modification of perioperative management for high-risk patients, to help prevent severe complications after liver resection for HCC.

ACKNOWLEDGMENTS

This work was supported by the grants from Taipei Medical University (TMU110-AE1-B11) and Ministry of Science and Technology, Taiwan, R.O.C. (MOST109-2314-B-038-024 and MOST104-2314-B-075-015).

REFERENCES

1. World Health Organization, International Agency for Research on Cancer. GLOBOCAN: Estimated cancer incidence, mortality and prevalence worldwide in 2020. Available at https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf. Accessed October 17, 2021.
2. Kudo M. Recent advances in systemic therapy for hepatocellular carcinoma in an aging society: 2020 update. *Liver Cancer* 2020;**9**:640–62.
3. Ishii M, Mizuguchi T, Harada K, Ota S, Meguro M, Ueki T, et al. Comprehensive review of post-liver resection surgical complications and a new universal classification and grading system. *World J Hepatol* 2014;**6**:745–51.
4. Yang T, Liu K, Liu CF, Zhong Q, Zhang J, Yu JJ, et al. Impact of postoperative infective complications on long-term survival after liver resection for hepatocellular carcinoma. *Br J Surg* 2019;**106**:1228–36.
5. Lin JA, Liao CC, Lee YJ, Wu CH, Huang WQ, Chen TL. Adverse outcomes after major surgery in patients with systemic lupus erythematosus: a nationwide population-based study. *Ann Rheum Dis* 2014;**73**:1646–51.
6. Tang F, Tie Y, Tu C, Wei X. Surgical trauma-induced immunosuppression in cancer: recent advances and the potential therapies. *Clin Transl Med* 2020;**10**:199–223.
7. Kim E, Kang JS, Han Y, Kim H, Kwon W, Kim JR, et al. Influence of preoperative nutritional status on clinical outcomes after pancreatoduodenectomy. *HPB (Oxford)* 2018;**20**:1051–61.
8. Lan H, Zhou L, Chi D, Zhou Q, Tang X, Zhu D, et al. Preoperative platelet to lymphocyte and neutrophil to lymphocyte ratios are independent prognostic factors for patients undergoing lung cancer radical surgery: a single institutional cohort study. *Oncotarget* 2017;**8**:35301–10.
9. Xia LJ, Li W, Zhai JC, Yan CW, Chen JB, Yang H. Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and prognostic nutritional index for predicting clinical outcomes in T1-2 rectal cancer. *BMC Cancer* 2020;**20**:208.
10. Xishan Z, Ye Z, Feiyan M, Liang X, Shikai W. The role of prognostic nutritional index for clinical outcomes of gastric cancer after total gastrectomy. *Sci Rep* 2020;**10**:17373.
11. Yu J, Hong B, Park JY, Hwang JH, Kim YK. Impact of prognostic nutritional index on postoperative pulmonary complications in radical cystectomy: a propensity score-matched analysis. *Ann Surg Oncol* 2021;**28**:1859–69.
12. Ke M, Xu T, Li N, Ren Y, Shi A, Lv Y, et al. Prognostic nutritional index predicts short-term outcomes after liver resection for hepatocellular carcinoma within the Milan criteria. *Oncotarget* 2016;**7**:81611–20.
13. Nagata S, Maeda S, Nagamatsu S, Kai S, Fukuyama Y, Korematsu S, et al. Prognostic nutritional index considering resection range is useful for predicting postoperative morbidity of hepatectomy. *J Gastrointest Surg* 2021;**25**:2788–95.
14. Sim JH, Jun IG, Moon YJ, Jeon AR, Kim SH, Kim B, et al. Association of preoperative prognostic nutritional index and postoperative acute kidney injury in patients who underwent hepatectomy for hepatocellular carcinoma. *J Pers Med* 2021;**11**:428.

15. Sim JH, Kim SH, Jun IG, Kang SJ, Kim B, Kim S, et al. The association between prognostic nutritional index (PNI) and intraoperative transfusion in patients undergoing hepatectomy for hepatocellular carcinoma: a retrospective cohort study. *Cancers (Basel)* 2021;**13**:2508.
16. Pinato DJ, North BV, Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). *Br J Cancer* 2012;**106**:1439–45.
17. Kamath PS, Kim WR; Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). *Hepatology* 2007;**45**:797–805.
18. Hiraoka A, Kumada T, Michitaka K, Toyoda H, Tada T, Ueki H, et al. Usefulness of albumin-bilirubin grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. *J Gastroenterol Hepatol* 2016;**31**:1031–6.
19. Vallet-Pichard A, Mallet V, Pol S. FIB-4: a simple, inexpensive and accurate marker of fibrosis in HCV-infected patients. *Hepatology* 2006;**44**:769.
20. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, Sánchez-Avila F, Vargas-Voráckova F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol* 2008;**7**:350–7.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205–13.
22. Yang T, Zhang J, Lu JH, Yang GS, Wu MC, Yu WF. Risk factors influencing postoperative outcomes of major hepatic resection of hepatocellular carcinoma for patients with underlying liver diseases. *World J Surg* 2011;**35**:2073–82.
23. Ercolani G, Grazi GL, Ravaioli M, Del Gaudio M, Gardini A, Cescon M, et al. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. *Ann Surg* 2003;**237**:536–43.
24. Arzumanyan A, Reis HM, Feitelson MA. Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma. *Nat Rev Cancer* 2013;**13**:123–35.
25. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol* 2015;**33**:550–8.
26. Tangkijvanich P, Anukulkarnkusol N, Suwangool P, Lertmaharit S, Hanvivatvong O, Kullavanijaya P, et al. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol* 2000;**31**:302–8.
27. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;**68**:723–50.
28. Abou-Alfa GK, Pawlik SJ, Vauthey JN. Liver. In: Amin MB, editor. AJCC Cancer Staging Manual. 8th ed. Chicago: AJCC; 2017, p. 287–93.
29. Ng IO, Lai EC, Ng MM, Fan ST. Tumor encapsulation in hepatocellular carcinoma. A pathologic study of 189 cases. *Cancer* 1992;**70**:45–9.
30. Poon RT, Fan ST, Ng IO, Wong J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. *Ann Surg* 2000;**231**:544–51.
31. Ho CM, Wakabayashi G, Nitta H, Ito N, Hasegawa Y, Takahara T. Systematic review of robotic liver resection. *Surg Endosc* 2013;**27**:732–9.
32. Chang WK, Lee MY, Tai YH, Kuo YM, Tsou MY, Chang KY. Does epidural analgesia improve the cancer outcome in hepatocellular carcinoma after resection surgery? A retrospective analysis. *J Chin Med Assoc* 2019;**82**:295–9.
33. Wu HL, Tai YH, Lin SP, Yang SH, Tsou MY, Chang KY. Epidural analgesia does not impact recurrence or mortality in patients after rectal cancer resection. *Sci Rep* 2021;**11**:913.
34. Tai YH, Wu HL, Mandell MS, Tsou MY, Chang KY. The association of allogeneic blood transfusion and the recurrence of hepatic cancer after surgical resection. *Anaesthesia* 2020;**75**:464–71.
35. Tai YH, Wu HL, Mandell MS, Lin SP, Tsou MY, Chang KY. The association of non-small cell lung cancer recurrence with allogenic blood transfusion after surgical resection: a propensity score analysis of 1,803 patients. *Eur J Cancer* 2020;**140**:45–54.
36. Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001;**54**:774–81.
37. YOUDEN WJ. Index for rating diagnostic tests. *Cancer* 1950;**3**:32–5.
38. Sperandei S. Understanding logistic regression analysis. *Biochem Med (Zagreb)* 2014;**24**:12–8.
39. McCluney SJ, Giakoustidis A, Segler A, Bissel J, Valente R, Hutchins RR, et al. Neutrophil: lymphocyte ratio as a method of predicting complications following hepatic resection for colorectal liver metastasis. *J Surg Oncol* 2018;**117**:1058–65.
40. Neal CP, Mann CD, Garcea G, Briggs CD, Dennison AR, Berry DP. Preoperative systemic inflammation and infectious complications after resection of colorectal liver metastases. *Arch Surg* 2011;**146**:471–8.
41. Song M, Graubard BI, Rabkin CS, Engels EA. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. *Sci Rep* 2021;**11**:464.
42. Goh BK, Kam JH, Lee SY, Chan CY, Allen JC, Jeyaraj P, et al. Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and prognostic nutrition index as preoperative predictors of early mortality after liver resection for huge (≥10 cm) hepatocellular carcinoma. *J Surg Oncol* 2016;**113**:621–7.
43. Chu MO, Shen CH, Chang TS, Xu HW, Yen CW, Lu SN, et al. Pretreatment inflammation-based markers predict survival outcomes in patients with early stage hepatocellular carcinoma after radiofrequency ablation. *Sci Rep* 2018;**8**:16611.
44. Wu HL, Kuo HC, Li CC, Wu YM, Lin SP, Chang KY, et al. A comparison of prognostic performance of perioperative inflammation markers in surgical resection for hepatocellular carcinoma. *J Chin Med Assoc* 2021;**84**:614–22.
45. Cools-Lartigue J, Spicer J, McDonald B, Gowing S, Chow S, Giannias B, et al. Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. *J Clin Invest* 2013;123:3446–58.
46. Mahmoud SM, Paish EC, Powe DG, Macmillan RD, Grainge MJ, Lee AH, et al. Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. *J Clin Oncol* 2011;**29**:1949–55.
47. Kitayama J, Yasuda K, Kawai K, Sunami E, Nagawa H. Circulating lymphocyte is an important determinant of the effectiveness of preoperative radiotherapy in advanced rectal cancer. *BMC Cancer* 2011;**11**:64.
48. Dupont G, Flory L, Morel J, Lukaszewicz AC, Patoir A, Presles E, et al. Postoperative lymphopenia: an independent risk factor for postoperative pneumonia after lung cancer surgery, results of a case-control study. *PLoS One* 2018;**13**:e0205237.
49. Duggan EW, Carlson K, Umpierrez GE. Perioperative hyperglycemia management: an update. *Anesthesiology* 2017;**126**:547–60.
50. Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. *Br J Anaesth* 2013;**110**:690–701.
51. Matsubara T, Takamori S, Haratake N, Fujishita T, Toyozawa R, Ito K, et al. Identification of the best prognostic marker among immunonutritional parameters using serum C-reactive protein and albumin in non-small cell lung cancer. *Ann Surg Oncol* 2021;**28**:3046–54.
52. Andres A, Toso C, Moldovan B, Schiffer E, Rubbia-Brandt L, Terraz S, et al. Complications of elective liver resections in a center with low mortality: a simple score to predict morbidity. *Arch Surg* 2011;**146**:1246–52.