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ORIGINAL RESEARCH

# Comparison of Prognostic Value of Red Cell-Related Parameters of Biliary Tract Cancer After Surgical Resection and Integration of a Prognostic Nomogram: A Retrospective Study

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## ABSTRACT

***Introduction***: Biliary tract cancer (BTC) comprises infrequently occurring neoplasms with poor prognoses. Red blood cell-related parameters are commonly reported prognostic factors. We aimed to compare and evaluate the clinical value of red blood cell-related parameters and develop a prognostic nomogram.

***Methods***: The analysis involved 418 patients with BTC who underwent surgery from December 2003 to April 2017. Patients were divided into training and validation cohorts. Red blood cell-related parameters were compared using Kaplan-Meier analysis, the area under receiver-operating characteristic curve (AUC), and C-index. Predictive abilities were evaluated using Cox regression. We developed a nomogram incorporating superior parameters verified using calibration curves, internal validation, and subgroup analysis. The nomogram was compared with the tumour-node-metastasis staging system through ROC, C-index, and Kaplan-Meier analysis.

***Results***: A combined parameter comprising haemoglobin, albumin, lymphocytes, and platelets (HALP), which was superior to other red blood cell-related parameters, indicated a high risk of worse overall survival when low. Univariate analysis revealed that HALP together with other clinical characteristics was associated with overall survival. Multivariate analysis revealed that HALP, tumour-node-metastasis staging, and operative outcome were independent predictors of poor overall survival. Internal validation proved the predictive value of the nomogram. Additional statistical analyses established the advantages of the nomogram vs. tumour-node-metastasis staging.

***Conclusion***: HALP was a superior red blood cell-related parameter and an independent predictor of prognosis. Our nomogram based on HALP, tumour-node-metastasis staging, and operative outcome is a promising model for predicting overall survival.

**Keywords:** Biliary tract cancer; HALP; Nomogram; Prognosis

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**Key Summary Points**

Red blood cell-related parameters are commonly reported prognostic factors for biliary tract cancer, although their value for biliary tract cancer (BTC) is unknown.

We aimed to compare and evaluate the clinical value of red blood cell-related parameters and to develop a prognostic nomogram.

A parameter combining haemoglobin, albumin, lymphocyte count, and platelet count (HALP) was a superior red blood cell-related parameter and an independent predictor of prognosis.

A nomogram based on HALP, tumour-node-metastasis staging, and operative outcome is a promising model for predicting overall survival.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13326563.

## INTRODUCTION

Biliary tract cancer (BTC) includes tumours of the gallbladder (GBC), cholangiocarcinoma (CCA) (intrahepatic [ICC] and extrahepatic bile duct [ECC]), and ampulla of Vater. Although BTC is rare, it is clinically significant because of its dismal outcome and limited therapeutic options [1–4]. The overall 1-, 3-, and 5-year relative survival rates, which have not significantly increased in recent decades, are 25.0%, 9.7%, and 6.8%, respectively [5]. Complete resection is the only available option to cure BTC, and only 10% of patients are diagnosed at an early stage and are thus considered for curative resection [6]. However, recurrence and progression to metastatic BTC commonly occur within 2 years after resection, which accounts for its poor prognosis [7, 8]. Consequently, we require an accurate patient stratification system to inform clinical decision-making as well as to establish the rationale for designing clinical trials. Such a stratification strategy requires an effective prognosis prediction model to serve as an important reference.

The most commonly used prognostic factor for BTC is tumour-node-metastasis (TNM) staging as defined by the American Joint Committee on Cancer (AJCC; 8th edition) [9]. TNM staging ranks the extent of a cancer by scoring the tumour, involved lymph nodes, and the presence or absence of metastasis. This method was developed for general cancer diagnosis and lacks personalized prediction of the prognosis of individual patients and does not consider other important prognostic parameters. Thus, we urgently require a resource to identify important clinical parameters that are effective for cancer prognosis as well as to compensate for the insufficiency of the BTC prognostic evaluation system.

Haematological markers predict the prognoses of different neoplasms. Among them, red blood cell-related parameters achieve ideal predictive ability as follows: haemoglobulin (HGB) [10]; red blood count (RBC) [11]; mean corpuscular volume (MCV) [12]; haematocrit (HCT) [13]; red blood distribution width (RDW) [14]; haemoglobin, albumin, lymphocyte, and platelet parameter (HALP) [15]; HGB-to-RDW ratio (HRR) [16]; HGB-to-platelet ratio (HPR). Red blood cell-related parameters reveal the physiological status of the circulatory system and are potentially associated with the outcomes of cancer. Specifically, HGB confers value for predicting the prognoses of patients with BTC [17]. However, the relationship between other parameters and prognosis, as well as outcomes of patients with BTC, is unclear. Moreover, no study compares the prognostic significance of red blood cell-related parameters.

Here, we aimed to investigate the prognostic role of red blood cell-related parameters of patients with BTC and to integrate superior parameters with other clinical variables to develop a nomogram to predict the prognosis of patients with BTC.

# METHODS

## Study Population

The study included 601 patients with BTC (including ICC, ECC, and GBC) who underwent resection at the Peking Union Medical College Hospital from January 2003 to September 2017. The inclusion criteria were as follows: (1) histologically confirmed BTC, (2) resectable BTC, (3) no history of other malignancies, and (4) clinical data available upon first diagnosis. These criteria were met by 418 patients whose data were included in the statistical analyses. Patients with missing follow-up data or with stage IV TNM, defined by the AJCC 8th staging system [6], were excluded from the study. Interval validation was performed by drawing a random sample of 30% patients from the original study population ($n$ = 418), using the Caret package in R 3.6.3.

The Medical Ethics Committees of Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College approved the study, which was conducted in accordance with the ethical standards of the World Medical Association's Declaration of Helsinki [18]. The requirement for informed consent was waived because this was a retrospective study.

## Data Collection

Clinical data including age, sex, jaundice, gallbladder stones, alcohol consumption, preoperative therapy, intraoperative haemorrhage, choice of operation, incision margins (R), maximum tumour diameter (D), TNM stage, surgical procedure, operative surgical outcome, chemotherapy, radiotherapy, postoperative complications, hospitalization days (HODs), and overall survival (OS) were collected from medical records. TNM stage was determined according to the 8th International AJCC criteria for BTC [6]. Laboratory data included alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and differential blood counts [platelet (PLT) and lymphocyte (LMY)]. Red blood cell-related parameters included HGB, RBC, MCV, HCT, RDW, HALP, HPR, and HRR. HALP was defined as (HGB*ALB*LMY)/PLT. HRR was defined as HGB/RDW, and HPR was defined as HGB/PLT.

## Statistical Analysis

Data for continuous variables are expressed as the mean ± standard deviation (SD). Comparisons of baseline characteristics between groups were performed using chi-square tests. Values of ALT, AST, ALB, PLT, LMY, CEA, CA 19-9, intraoperative haemorrhage, and $D$ were divided into high and low groups according to our hospitals' routine convention. The optimal cut-off values for red blood cell-related parameters were established using X-tile software. We used the Kaplan-Meier method to compare the relationship between red blood cell-related parameters to long-term OS. The prognostic abilities of red blood cell-related parameters were evaluated using the areas under the receiver-operating characteristic (ROC) curves (AUC) and C-index. Univariate and multivariate Cox regression analyses of potential factors affecting patients' outcomes were performed. The effect of HALP on OS as a function of other parameters was investigated using JMP software (version Professional 13; SAS Institute, Cary, NC, USA). ROC curves were generated to verify the accuracy of HALP and other significant factors associated with therapeutic effects as well as to predict OS.

Based on multivariate analysis of a training cohort, a nomogram was developed using the rms package in R version 3.6.3. The performance of the nomogram was assessed using a calibration curve. The prognostic abilities of the nomogram were compared with HALP alone,

extent of radical resection alone, and TNM stage by comparing AUC values and the C-index. The Kaplan-Meier (K-M) method was applied to subgroups defined by carcinoma type and extent of radical resection to further validate the prognostic effect of superior parameters and the nomogram. The comparison of the performance of the nomogram compared with that of the TNM staging system was performed using same method.

Statistical analysis was conducted using R 3.6.3 software (Institute for Statistics and Mathematics, Vienna, Austria) and the Statistical Package for Social Sciences version 25.0 (SPSS, Chicago, IL, USA). Significance levels were defined as $P < 0.05$ (two-sided).

## RESULTS

### Patients' Characteristics

The baseline characteristics of 287 and 131 patients included in the training and validation cohorts, respectively, are listed in Table 1. The GBC, ECC, and ICC groups each comprised 23%, 56%, and 21% of the patient population. The median OS of the training cohort was 19 (9–37) months and that of the validation cohort was 18 (10–38) months. Radical resection was performed on 36% of patients in each cohort. TNM stages were as follows: 37%, stage I; 32%, stage II; 31%, stage III. Postoperative complications were experienced by 113 (39%) and 49 (37%) patients in the training and validation cohorts, respectively.

Cholecystectomy was performed on 95% of patients with GBC, 51% of whom underwent concurrent lymphadenectomy. In accordance with the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology, 27% of patients with TNM stage III GBC underwent partial or segmental hepatectomy, 22% of patients with ECC underwent cholecystectomy, and 31% underwent bile duct resection. Among the patients with mid-bile duct ECC, 38% underwent pancreaticoduodenectomy. Among 89% of patients with ICC who underwent partial or segmental hepatectomy, 34% underwent concurrent cholecystectomy.

**Table 1** Clinicopathological characteristics of 420 patients with cancer of the biliary system

| | **Training cohort medium (IQR) or *n* (%)** | **Validation cohort medium (IQR) or *n* (%)** |
|---|---|---|
| Total | 287 | 131 |
| Disease type | | |
| GBC | 68 (24) | 26 (20) |
| ECC | 162 (56) | 74 (56) |
| ICC | 57 (20) | 31 (24) |
| Age (years) | | |
| ≤ 60 | 130 (45) | 56 (42) |
| > 60 | 157 (55) | 75 (58) |
| Sex | | |
| Male | 125 (43) | 55 (42) |
| Female | 162 (57) | 76 (58) |
| Jaundice | | |
| No | 119 (42) | 56 (43) |
| Yes | 168 (58) | 75 (57) |
| Gallbladder stone | | |
| No | 181 (53) | 82 (75) |
| Yes | 76 (47) | 27 (25) |
| Alcohol | | |
| No | 212 (74) | 101 (77) |
| Yes | 74 (26) | 30 (23) |
| ALT (U/l) | | |
| ≤ 40 | 90 (32) | 54 (42) |
| > 40 | 197 (68) | 77 (58) |
| AST (U/l) | | |
| ≤ 40 | 103 (38) | 49 (39) |
| > 40 | 171 (62) | 79 (61) |
| ALB (g/l) | | |
| ≤ 40 | 111 (39) | 52 (39) |
| > 40 | 176 (61) | 79 (61) |

**Table 1** continued

| | Training cohort medium (IQR) or *n* (%) | Validation cohort medium (IQR) or *n* (%) |
|---|---|---|
| PLT ($\times 10^9$/l) | | |
| $\leq 300$ | 234 (82) | 101 (77) |
| $> 300$ | 53 (18) | 30 (23) |
| LMY ($\times 10^9$/l) | | |
| $\leq 1.00$ | 239 (83) | 115 (88) |
| $> 1.00$ | 48 (17) | 16 (12) |
| CEA (mg/l) | | |
| $\leq 5$ | 237 (83) | 98 (75) |
| $> 5$ | 50 (17) | 33 (25) |
| CA199 (U/ml) | | |
| $\leq 1000$ | 252 (88) | 110 (84) |
| $> 1000$ | 35 (12) | 21 (16) |
| Surgical procedure | | |
| Cholecystectomy | 124 (43) | 48 (39) |
| Bile duct resection | 69 (24) | 27 (22) |
| Pancreaticoduodenectomy | 64 (22) | 28 (23) |
| Hepatectomy | 72 (25) | 34 (28) |
| Lymphadenectomy | 63 (22) | 28 (23) |
| Chemotherapy | | |
| No | 182 (83) | 87 (84) |
| Yes | 38 (17) | 17 (16) |
| Radiotherapy | | |
| No | 206 (94) | 96 (92) |
| Yes | 14 (6) | 8 (8) |
| Intraoperative haemorrhage (ml) | | |
| $\leq 400$ | 160 (56) | 80 (58) |
| $> 400$ | 96 (44) | 44 (42) |
| Margin | | |
| R0 | 134 (47) | 75 (57) |
| R1 | 151 (53) | 56 (43) |

**Table 1** continued

| | Training cohort medium (IQR) or *n* (%) | Validation cohort medium (IQR) or *n* (%) |
|---|---|---|
| *D* (cm) | | |
| $\leq 5$ | 245 (86) | 111 (89) |
| $> 5$ | 41 (14) | 13 (11) |
| TNM | | |
| I | 104 (36) | 53 (40) |
| II | 92 (32) | 40 (31) |
| III | 91 (32) | 38 (29) |
| Operation outcome | | |
| Radical | 104 (36) | 47 (37) |
| Non-radical | 182 (64) | 81 (63) |
| Postoperative complications | | |
| No | 174 (61) | 83 (63) |
| Yes | 113 (39) | 49 (37) |
| HOD (days) | 26.1 ($\pm$ 1.0) | 29.0 ($\pm$ 2.7) |
| OS (months) | 19 (9–37) | 18 (10–38) |
| HGB (g/l) | | |
| $\leq 142$ | 67 (24) | 27 (21) |
| $> 142$ | 220 (76) | 104 (79) |
| RBC ($\times 10^{12}$/l) | | |
| $\leq 4.39$ | 106 (37) | 85 (84) |
| $> 4.39$ | 181 (63) | 46 (36) |
| MCV (fl) | | |
| $\leq 87.2$ | 239 (84) | 25 (19) |
| $> 87.2$ | 47 (16) | 106 (81) |
| HCT (l/l) | | |
| $\leq 41.9$ | 68 (24) | 100 (77) |
| $> 41.9$ | 218 (76) | 31 (23) |
| RDW (%) | | |
| $\leq 14.3$ | 157 (55) | 68 (52) |
| $> 14.3$ | 128 (45) | 63 (48) |

**Table 1** continued

| | Training cohort medium (IQR) or *n* (%) | Validation cohort medium (IQR) or *n* (%) |
|---|---|---|
| HALP | | |
| ≤ 42.68 | 81 (29) | 47 (36) |
| > 42.68 | 206 (71) | 84 (64) |
| HRR | | |
| ≤ 9.40 | 129 (45) | 76 (58) |
| > 9.40 | 156 (55) | 55 (42) |
| HPR | | |
| ≤ 0.44 | 218 (76) | 35 (27) |
| > 0.44 | 69 (24) | 96 (73) |

*GBC*, gallbladder carcinoma; *ICC*, intrahepatic cholangiocarcinoma; *ECC*, extrahepatic cholangiocarcinoma; *TNM*, tumour-node-metastasis; *HGB*, haemoglobulin; *RBC*, red blood count; *MCV*, mean corpuscular volume; *HCT*, haematocrit; *RDW*, red blood distribution width; *HALP*, haemoglobin, albumin, lymphocyte, and platelet parameter; *HRR*, HGB-to-RDW ratio; *HPR*, HGB-to-platelet ratio; *R*, incision margins; *D*, maximum tumour diameter; *HOD*, hospitalization day; *OS*, overall survival; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *ALB*, albumin; *CEA*, carcinoembryonic antigen; *CA 19–9*, carbohydrate antigen 19–9; *PLT*, platelet; *LMY*, lymphocyte; *SD*, standard deviation; *AUC*, areas under the ROC curves; *HR*, hazard ratio; *CI*, confidence interval; *PLR*, PLT-to-LMY ratio; *GPS*, Glasgow prognostic score

## Comparison of Red Blood Cell-Related Parameters

Kaplan-Meier curves stratified according to red blood cell-related parameters are shown in Fig. 1. All parameters were associated with the OS of patients in the training cohort. AUC values after 1, 3, and 5 years were calculated to compare the predictive value of red blood cell-related parameters (Fig. S1). Time-dependent ROC curves were generated to compare the performances of these risk factors (Fig. 2). The three superior risk factors were HRR (C-index = 0.566), HALP (C-index = 0.562), and HGB (C-index = 0.556). The subgroup analyses of the associations of HALP, HGB, and HRR with OR are presented in Fig. S2. Only HALP significantly correlated with the OS of each subgroup and was the superior parameter overall.

Univariate Cox analysis revealed that OS was significantly associated with jaundice, LMY ≤ 1.0, HGB ≤ 142, RBC ≤ 4.39, MCV ≤ 87.2, HCT ≤ 41.9, RDW > 14.3, HALP ≤ 42.68, HRR ≤ 9.40, HPR ≤ 0.018, CEA > 5 ng/ml, CA 19–9 > 1000 U/ml, TNM stage, and extent of radical resection. Multivariate analysis identified the independent factors associated with poor OS as follows: HALP ≤ 42.68 [hazard ratio (HR) 1.548; 95% confidence interval (Cl) 1.017–2.285; $P = 0.041$], TNM stage (HR 1.393; 95% Cl 1.000–1.941; $P = 0.050$), and nonradical resection (HR 2.258; 95% Cl 1.625–3.136; $P < 0.001$; Table 2). Internal validation yielded results similar to those of the training cohort.

Internal validation (Fig. S3) indicated that low HALP was related to poor postoperative outcomes ($P < 0.001$). Further analysis based on patient stratification according to disease type and extent of radical resection indicated HALP's predictive value (GBC group, $P = 0.016$; ECC group, $P = 0.014$; ICC group, $P = 0.010$; nonradical group, $P = 0.041$; radical group, $P < 0.001$; Fig. S4).

## Relationship Between HALP and Patients' Clinical Characteristics

We divided patients into a high and a low group according to the cut-off value of each parameter. Patients' characteristics in each group are summarized in Table 3. The frequency of jaundice was higher in the high-HALP group vs. the low-HALP group (34.6% vs. 68.0%, respectively, $P < 0.001$), and the proportion of patients with higher ALT or AST was larger in the low-HALP group vs. the high-HALP group. Red blood cell-related parameters including RBC, HCT, and RDW were higher in the high-HALP group vs. the low-HALP group.

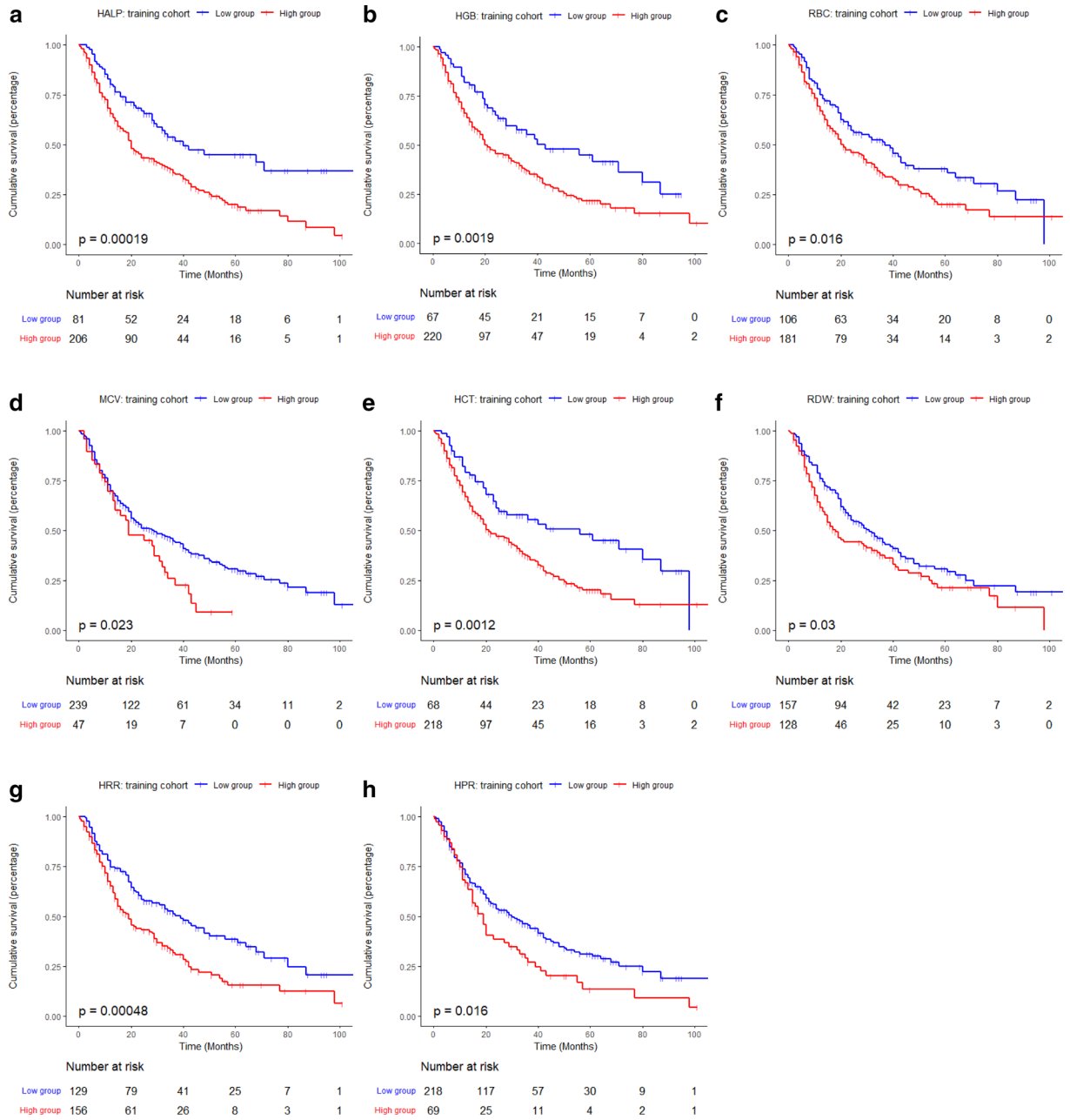


**Fig. 1** Kaplan-Meier analysis of OS stratified according to red blood cell-related parameters of the training cohort. K-M curves stratified according to **a** HALP, **b** HGB, **c** RBC, **d** RDW, **e** HCT, **f** MCV, **g** HRR, and **h** HPR

## Nomogram Development and Validation

Multivariate Cox regression analysis identified HALP, TNM stage, and operative outcome as independent predictors of prognosis of BTC (Table 2). The model that incorporated the above independent parameters is presented as Nomogram A (Fig. 3a). The 1-, 3-, and 5-year calibration curves for predicting OS using the nomogram demonstrated good agreement with the actual observations (Fig. 3b). As established above, HALP was the superior potential risk factor for predicting overall survival. When we developed Nomogram B without HALP (Fig. 3c,

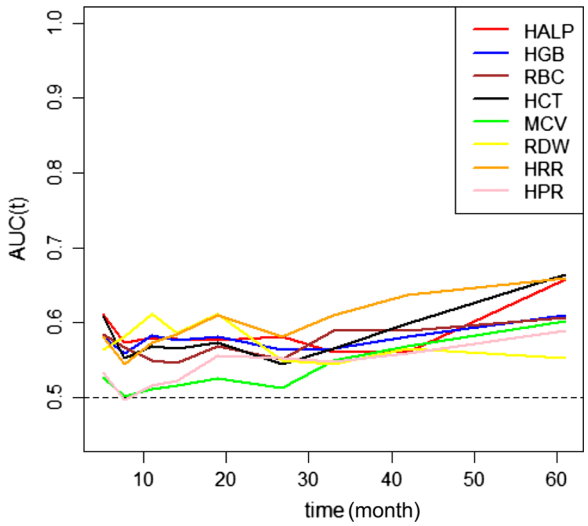


**Fig. 2** ROC analysis of red blood cell-related parameters of the training cohort

d) to further evaluate its predictive value, we found that the calibration curves were not significantly different.

Analysis according to stratification of disease type and operative outcome (Fig. S5) indicated Nomogram A's superior predictive value HALP; nonradical group, $P < 0.001$; radical group, $P = 0.022$).

### Comparison of Predictive Value Determined Using Nomograms A and B, Risk Factors, and TNM Stage

The AUROC curves after 1, 3, and 5 years OS and C-indexes were generated to compare the performances of Nomograms A and B, HALP, operative outcome, and TNM stage (Table S1). Time-dependent ROC curves display the difference between these models and variables (Fig. 3e). In the training cohort, the C-index for predicting OS was 0.656 using Nomogram A vs. 0.633 using Nomogram B (C-index = 0.633), HALP (C-index = 0.562, $P < 0.001$), radical extent (C-index = 0.612, $P = 0.024$), and TNM stage (C-index = 0.562, $P < 0.001$). Nomogram A showed an advantage vs. Nomogram B (IDI = 2.92%, $P = 0.007$), which demonstrates the effect of HALP. Internal validation results were similar to those of the training cohort.

Compared with the TNM staging system, 59% of patients were regraded using the nomogram; 22% were downstaged and 37% were upstaged (Table 4). Among the disease subgroups, > 80% of patients in the ECC group had the most significant change of prognostic risk grade. Patients who underwent radical resection underwent more change in stages than the nonradical group (Table S2). The above difference demonstrated the improvement on discrimination ability over the TNM staging system.

Specifically, the TNM stage system and Nomogram A showed good ability to stratify prognoses of the overall population, and the results of subgroup analysis differed between the two models (Fig. 4). When stratified according to disease type (Fig. 4b–d), Nomogram A achieved a significant prognostic effect in the subgroups as follows: GBC, $P < 0.001$; ECC, $P < 0.001$; ICC, $P < 0.001$. The TNM staging system showed a prognostic effect only in the GBC ($P < 0.001$) and ICC ($P < 0.001$) groups and lacked predictive value for ECC patients ($P = 0.180$). Nomogram A also showed an advantage vs. TNM stage in the nonradical and radical groups.

## DISCUSSION

The prognosis of patients with BTC, which includes CCA, GBC, and ampulla cancer, is poor, in part because of the paucity of treatment options. Accurate prediction of BTC prognosis will likely benefit clinical decision-making for implementing personalized treatment after surgery. Red blood cell-related parameters serve as cancer prognostic factors, although their value for BTC is unclear. Here we aimed to compare and assess the prognostic value of different red blood cell-related parameters and to design a prognostic nomogram for BTC. Our results show that HALP was one of the superior red blood cell-related parameters for predicting prognosis. Moreover, we found that a lower HALP value, late TNM stage, and nonradical resection were independent predictors of prognosis. According to the score of each clinical variable, our nomogram model accurately

**Table 2** Univariate and multivariate Cox proportional hazard analyses of factors associated with overall survival

| | Training cohort | | | | | | Validation cohort | | |
|---|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | | Multivariate analysis | | | Multivariate analysis | | |
| | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI |
| Age (years) | | | | | | | | | |
| ≤ 60 | | 1.000 | | | | | | | |
| > 60 | 0.138 | 1.249 | 0.931–1.577 | | | | | | |
| Sex | | | | | | | | | |
| Female | | 1.000 | | | | | | | |
| Male | 0.997 | 0.999 | 0.744–1.343 | | | | | | |
| BMI | | | | | | | | | |
| > 25 | | 1.000 | | | | | | | |
| ≤ 25 | 0.369 | 1.160 | 0.839–1.603 | | | | | | |
| Jaundice | | | | | | | | | |
| No | | 1.000 | | | 1.000 | | | 1.000 | |
| Yes | 0.013 | 1.474 | 1.087–2.000 | 0.652 | 1.100 | 0.726–1.666 | 0.253 | 1.426 | 0.776–2.623 |
| Gallbladder stone | | | | | | | | | |
| No | | 1.000 | | | | | | | |
| Yes | 0.227 | 1.194 | 0.896–1.591 | | | | | | |
| ALT (U/l) | | | | | | | | | |
| ≤ 40 | | 1.000 | | | | | | | |
| > 40 | 0.126 | 1.240 | 0.941–1.634 | | | | | | |
| AST (U/l) | | | | | | | | | |
| ≤ 40 | | 1.000 | | | | | | | |
| > 40 | 0.059 | 1.303 | 0.990–1.715 | | | | | | |
| ALB (g/l) | | | | | | | | | |
| > 35 | | 1.000 | | | | | | | |
| ≤ 35 | 0.055 | 1.349 | 0.993–1.833 | | | | | | |
| PLT ($\times 10^9$/l) | | | | | | | | | |
| ≤ 300 | | 1.000 | | | | | | | |
| > 300 | 0.219 | 1.250 | 0.876–1.927 | | | | | | |
| LMY ($\times 10^9$/l) | | | | | | | | | |
| > 1.0 | | 1.000 | | | 1.000 | | | 1.000 | |
| ≤ 1.0 | 0.021 | 1.530 | 1.066–2.196 | 0.335 | 0.817 | 0.541–1.233 | 0.531 | 0.765 | 0.331–1.770 |

**Table 2** continued

| | Training cohort | | | | | | Validation cohort | | |
|---|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | | Multivariate analysis | | | Multivariate analysis | | |
| | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI |
| HGB (g/l) | | | | | | | | | |
| > 142 | | 1.000 | | | 1.000 | | | 1.000 | |
| ≤ 142 | 0.002 | 1.774 | 1.223–2.572 | 0.360 | 1.379 | 0.693–2.742 | 0.479 | 0.711 | 0.276–1.831 |
| RBC ($\times 10^{12}$/l) | | | | | | | | | |
| > 4.39 | | 1.000 | | | 1.000 | | | 1.000 | |
| ≤ 4.39 | 0.018 | 1.448 | 1.065–1.971 | 0.367 | 0.828 | 0.548–1.249 | 0.274 | 1.644 | 0.675–4.004 |
| MCV (fl) | | | | | | | | | |
| > 87.2 | | 1.000 | | | 1.000 | | | 1.000 | |
| ≤ 87.2 | 0.026 | 1.528 | 1.052–2.220 | 0.159 | 0.745 | 0.494–1.122 | 0.672 | 1.145 | 0.612–2.144 |
| HCT (l/l) | | | | | | | | | |
| > 41.9 | | 1.000 | | | 1.000 | | | 1.000 | |
| ≤ 41.9 | 0.002 | 1.820 | 1.257–2.636 | 0.300 | 0.706 | 0.366–1.364 | 0.164 | 0.543 | 0.229–1.284 |
| RDW (%) | | | | | | | | | |
| ≤ 14.3 | | 1.000 | | | 1.000 | | | 1.000 | |
| > 14.3 | 0.032 | 1.377 | 1.028–1.847 | 0.708 | 1.095 | 0.731–1.640 | 0.149 | 1.656 | 0.835–3.285 |
| HALP | | | | | | | | | |
| > 42.68 | | 1.000 | | | 1.000 | | | 1.000 | |
| ≤ 42.68 | < 0.001 | 1.924 | 1.352–2.738 | 0.041 | 1.548 | 1.017–2.285 | 0.005 | 2.400 | 1.296–4.445 |
| HRR | | | | | | | | | |
| > 9.40 | | 1.000 | | | 1.000 | | | 1.000 | |
| ≤ 9.40 | 0.001 | 1.685 | 1.249–2.274 | 0.487 | 1.187 | 0.732–1.927 | 0.958 | 0.977 | 0417–2.291 |
| HPR | | | | | | | | | |
| > 0.44 | | 1.000 | | | 1.000 | | | 1.000 | |
| ≤ 0.44 | 0.018 | 0.479 | 1.068–2.049 | 0.949 | 0.983 | 0.586–1.650 | 0.358 | 1.659 | 0.563–4.888 |
| CEA (mg/l) | | | | | | | | | |
| ≤ 5 | | 1.000 | | | 1.000 | | | 1.000 | |
| > 5 | 0.008 | 1.634 | 1.138–2.346 | 0.296 | 1.235 | 0.831–1.835 | 0.085 | 1.625 | 0.936–2.821 |
| CA19-9 (U/ml) | | | | | | | | | |
| ≤ 1000 | | 1.000 | | | 1.000 | | | 1.000 | |
| > 1000 | < 0.001 | 2.237 | 1.506–3.321 | 0.226 | 1.327 | 0.840–2.096 | 0.358 | 1.412 | 0.677–2.944 |

**Table 2** continued

| | Training cohort | | | | | | Validation cohort | | |
|---|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | | Multivariate analysis | | | Multivariate analysis | | |
| | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI |
| Haemorrhage (ml) | | | | | | | | | |
| ≤ 400 | | 1.000 | | | | | | | |
| > 400 | 0.896 | 1.019 | 0.765–1.358 | | | | | | |
| Margins | | | | | | | | | |
| R0 | | 1.000 | | | | | | 1.000 | |
| R1 | 0.297 | 1.168 | 0.872–1.565 | | | | 0.438 | 1.195 | 0.761–1.877 |
| *D* (cm) | | | | | | | | | |
| ≤ 5 | | 1.000 | | | | | | | |
| > 5 | 0.107 | 1.445 | 0.923–2.262 | | | | | | |
| TNM | | | | | | | | | |
| I + II | | 1.000 | | | 1.000 | | | 1.000 | |
| III | < 0.001 | 1.725 | 1.272–2.339 | 0.050 | 1.393 | 1.000–1.941 | 0.020 | 1.985 | 1.114–3.534 |
| Chemotherapy | | | | | | | | | |
| No | | 1.000 | | | | | | | |
| Yes | 0.839 | 1.045 | 0.685–1.594 | | | | | | |
| Operation outcome | | | | | | | | | |
| Radical | | 1.000 | | | 1.000 | | | 1.000 | |
| Non | < 0.001 | 2.344 | 1.742–3.154 | < 0.001 | 2.258 | 1.625–3.136 | < 0.001 | 2.706 | 1.664–4.398 |

*TNM*, tumour-node-metastasis; *HGB*, haemoglobulin; *RBC*, red blood count; *MCV*, mean corpuscular volume; *HCT*, haematocrit; *RDW*, red blood distribution width; *HALP*, haemoglobin, albumin, lymphocyte, and platelet parameter; *HRR*, HGB-to-RDW ratio; *HPR*, HGB-to-platelet ratio; *R*, incision margins; *D*, maximum tumour diameter; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *ALB*, albumin; *CEA*, carcinoembryonic antigen; *CA 19–9*, carbohydrate antigen 19–9; *PLT*, platelet; *LMY*, lymphocyte

predicted the 1-, 3-, and 5-year probabilities of survival of patients with BTC. This nomogram may therefore serve as a reference for patient stratification and clinical decision-making.

Haematological markers predict the prognosis of patients with neoplasms. Among them, the use of red blood cell-related parameters achieves an ideal predictive ability. HGB and RBC are used to develop nomograms for predicting cancer prognosis [10, 11]. For example, patients with oesophageal cancer with high MCV values have poorer prognoses [12], and there is a significant association between low HCT values and high risk of poor prognosis of patients with lung cancer [13]. Furthermore, elevated RDW values are associated with the prognosis of lung cancer [14]. Low HRR values are associated with late tumour stage [16]. Red blood cell-related parameters reveal the physiological status of the circulatory system and are potentially associated with the outcomes of patients with cancer. For example, a study on

**Table 3** Clinical characteristics of the patients associated with HALP

| Total | Training cohort medium (IQR) or *n* (%) | | | Validation cohort medium (IQR) or *n* (%) | | |
|---|---|---|---|---|---|---|
| | Low group | High group | *P* | Low group | High group | *P* |
| Age (years) | | | | | | |
| ≤ 60 | 40 (49.4) | 90 (43.7) | 0.383 | 21 (44.7) | 35 (41.7) | 0.738 |
| > 60 | 41 (50.6) | 116 (56.3) | | 26 (55.3) | 49 (58.3) | |
| Sex | | | | | | |
| Male | 30 (37.0) | 95 (46.1) | 0.163 | 15 (31.9) | 40 (47.6) | 0.081 |
| Female | 51 (63.0) | 111 (53.9) | | 32 (68.1) | 44 (52.4) | |
| Jaundice | | | | | | |
| No | 53 (65.4) | 66 (32.0) | **< 0.001** | 25 (53.2) | 32 (36.9) | 0.071 |
| Yes | 28 (34.6) | 140 (68.0) | | 22 (46.8) | 53 (63.1) | |
| Gallbladder stone | | | | | | |
| No | 52 (64.2) | 129 (62.6) | 0.902 | 33 (70.2) | 49 (58.3) | 0.158 |
| Yes | 20 (24.7) | 56 (27.2) | | 10 (21.3) | 18 (20.2) | |
| Alcohol | | | | | | |
| No | 58 (71.6) | 154 (75.1) | 0.541 | 34 (72.3) | 67 (79.8) | 0.332 |
| Yes | 23 (28.4) | 51 (24.9) | | 13 (27.7) | 17 (20.2) | |
| ALT (U/l) | | | | | | |
| ≤ 40 | 37 (45.7) | 53 (25.7) | **0.001** | 20 (42.6) | 34 (40.5) | 0.817 |
| > 40 | 44 (54.3) | 153 (74.3) | | 27 (57.4) | 50 (59.5) | |
| AST (U/l) | | | | | | |
| ≤ 40 | 42 (53.2) | 61 (31.3) | **0.001** | 20 (42.6) | 29 (35.8) | 0.449 |
| > 40 | 37 (46.8) | 134 (68.7) | | 27 (57.4) | 52 (64.2) | |
| CEA (mg/l) | | | | | | |
| ≤ 5 | 69 (85.2) | 168 (81.6) | 0.465 | 35 (74.5) | 63 (75.0) | 0.946 |
| > 5 | 12 (14.8) | 38 (18.4) | | 12 (25.5) | 21 (25.0) | |
| CA19-9 (U/ml) | | | | | | |
| ≤ 1000 | 75 (92.6) | 177 (85.9) | 0.120 | 40 (85.1) | 70 (83.3) | 0.791 |
| > 1000 | 6 (7.4) | 29 (14.1) | | 7 (14.9) | 14 (16.7) | |
| *D* (cm) | | | | | | |
| ≤ 5 | 64 (83.1) | 181 (91.0) | 0.064 | 38 (80.9) | 73 (86.9) | 0.072 |
| > 5 | 13 (16.9) | 18 (9.0) | | 8 (17.0) | 5 (6.0) | |

**Table 3** continued

| Total | Training cohort medium (IQR) or *n* (%) | | | Validation cohort medium (IQR) or *n* (%) | | |
|---|---|---|---|---|---|---|
| | Low group | High group | *P* | Low group | High group | *P* |
| TNM | | | | | | |
| I + II | 52 (64.2) | 143 (69.4) | 0.394 | 32 (68.1) | 61 (72.6) | 0.583 |
| III | 29 (35.8) | 63 (30.6) | | 15 (31.9) | 23 (27.4) | |
| RBC ($\times 10^{12}$/l) | | | | | | |
| > 4.39 | 49 (60.5) | 57 (27.7) | **< 0.001** | 19 (40.4) | 66 (78.6) | **< 0.001** |
| ≤ 4.39 | 32 (39.5) | 149 (72.3) | | 28 (59.6) | 19 (21.4) | |
| MCV (fl) | | | | | | |
| > 87.2 | 70 (86.4) | 169 (82.4) | 0.413 | 6 (12.8) | 19 (22.6) | 0.169 |
| ≤ 87.2 | 11 (13.6) | 36 (17.6) | | 41 (87.2) | 65 (77.4) | |
| HCT (l/l) | | | | | | |
| > 41.9 | 35 (43.2) | 33 (16.1) | **< 0.001** | 28 (59.6) | 72 (85.7) | **0.001** |
| ≤ 41.9 | 46 (56.8) | 172 (83.9) | | 19 (40.4) | 12 (14.3) | |
| RDW (%) | | | | | | |
| ≤ 14.3 | 58 (72.5) | 99 (48.3) | **< 0.001** | 28 (59.6) | 40 (47.6) | 0.189 |
| > 14.3 | 22 (27.5) | 106 (51.7) | | 19 (40.4) | 44 (52.4) | |

Bold represents $P < 0.05$

*TNM*, tumour-node-metastasis; *HGB*, haemoglobulin; *RBC*, red blood count; *MCV*, mean corpuscular volume; *HCT*, haematocrit; *RDW*, red blood distribution width; *HALP*, haemoglobin, albumin, lymphocyte, and platelet parameter; *HRR*, HGB-to-RDW ratio; *HPR*, HGB-to-platelet ratio; *R*, incision margins; *D*, maximum tumour diameter; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *ALB*, albumin; *CEA*, carcinoembryonic antigen; *CA 19-9*, carbohydrate antigen 19–9; *PLT*, platelet; *LMY*, lymphocyte

the modelling of clinical parameters to develop a nomogram for patients with BTC employed HGB as an independent prognostic parameter [17]. Together, these studies indicate the potential clinical value of red blood cell-related parameters that are associated with the prognoses of patients with BTC.

Compared with other red blood cell-related parameters, HALP combines more haematological parameters to provide a more comprehensive assessment of health. Here, we show that a low HALP value significantly correlated with a poor prognostic outcome, which was further associated with low HGB and ALB and a significantly higher PLT-to-LMY ratio (PLR). Other studies show predictive value of these three risk factors. Low HGB is a standard marker for cancer-related anaemia [19], and multiple studies found a significant relationship between low HGB and poor surgical outcomes of patients with cancer [20, 21].

Hypoalbuminaemia serves as a nutritional-deficiency index because it significantly affects the synthesis of visceral proteins. Furthermore, low serum ALB serves to stratify BTC patients into different prognostic categories after surgical resection [22] and the Glasgow prognostic score (GPS) is an independent factor for predicting prognosis of BTC [23].

Systemic inflammation, represented by elevated PLR, enhances the angiogenesis, immunosuppression, and metastasis associated

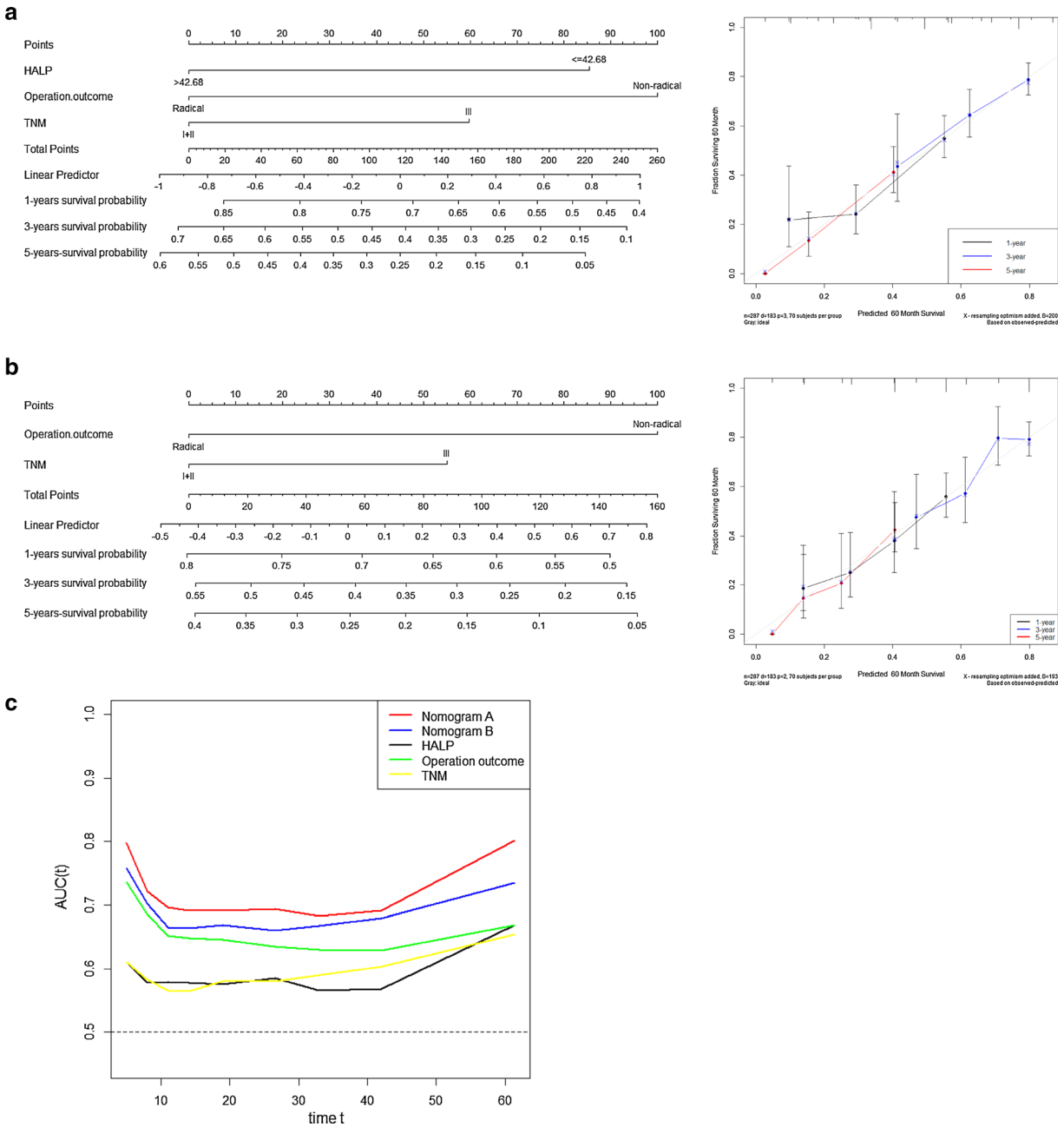


**Fig. 3** Nomogram to predict the probability of survival and comparison of different models. **a** Nomogram A for OS. Calibration curve for Nomogram A. **b** Nomogram B for OS, including risk factors in Nomogram A except HALP. Calibration curve for Nomogram B. **c** ROC analysis of prognosis prediction models of the training cohort

with tumour cells. Furthermore, infiltration of tumours by platelets is associated with improved accuracy of predicting the prognosis of patients with BTC. Systemic inflammation represented by PLR predicts the OS of patients with advanced BTC who undergo palliative chemotherapy [24]. Combined with the Cox regression results, we show here that the combination of these three factors serve as an independent predictor of prognosis of BTC and

**Table 4** Comparison of cancer staging between the AJCC Staging Manual (8th edition) and Nomogram A

| | AJCC staging system, 8th edition | | | Total |
|---|---|---|---|---|
| | I | II | III | |
| Nomogram A | | | | |
| Low | 39 | 19 | 27 | 85 |
| | 45.9% | 22.3% | 31.8% | 20.6% |
| Medium | 80 | 73 | 45 | 198 |
| | 40.4% | 36.9% | 22.7% | 48.1% |
| High | 37 | 35 | 57 | 129 |
| | 28.6% | 27.1% | 44.2% | 31.3% |
| Total | 156 | 127 | 129 | 412 |

*AJCC*, American Joint Committee on Cancer

that HALP is superior for this purpose than each alone. Moreover, low HALP predicted poor prognosis of patients with BTC based on possible complications of cancer-related anaemia, malnutrition, and systemic inflammation (Fig. S6).

Anaemia may lead to resistance to postoperative gemcitabine therapy [25]. Furthermore, patients suffering from malnutrition during the early stage of BTC benefit from nutritional intervention, which improves prognosis [26]. Systemic inflammation affects the outcome of palliative chemotherapy [24]. The significant predictive value of HALP indicates that more attention should be preoperatively directed to assessing anaemia, malnutrition, and inflammation of patients before surgery. Moreover, early intervention will likely ameliorate these symptoms to improve the OS of patients with BTC.

Clinical parameters that influence HALP include jaundice, ALT, AST, RBC, HCT, and RDW. Preoperative jaundice indicates a higher risk of postoperative complications and adverse events, which indicates poor prognosis [27]. Elevated levels of ALT and AST, which are produced by hepatocyte, are associated with hepatic damage, indicating liver disease and singular body metabolism. Such damage may lead to abnormalities in haematological parameters such as HALP. Low levels of RBCs and HCT are markers of anaemia, which is revealed as well by low values of HALP. Conversely, significantly elevated RDW values reflect the heterogeneity of red blood cells, which correlate with iron deficiency anaemia and lead to low values of HALP.

TNM stage, as defined by the AJCC, is the most widely used prognostic model for BTC. However, the TNM staging system is designed for broad cancer diagnosis and does not include a requirement for examining individual patients. We show here that in the ECC subgroup and radical group, Nomogram A significantly improved the discriminative power of the TNM staging system. Furthermore, > 60% of patients' risk grade was upstaged in the ECC group, and approximately 60% of patients' risk grades changed in the radical group. These findings suggest that the TNM staging system requires specific prognostic parameters to accommodate different types of diseases and interventions.

Compared with the TNM stage model defined by the AJCC (8th edition), we show here that adding more clinical factors significantly improved the accuracy and discriminative power of prediction. Our nomogram, which combined HALP, TNM stage, and operative outcome, achieved significant value for predicting OS. Furthermore, HALP and operative outcome contributed to a better prognostic model by adding patient-specific characteristics. The AURIC and C-index have advantages over the TNM staging system, and K-M analysis of subgroups further improved of the performance of Nomogram A.

Our study has several limitations. First, the predictive effect was ascertained using only internal validation, which may lead to selection bias that affects the generalization of our results acquired using the model. Second, because of the small number of patients, we analysed several clinical factors. Future research analysing more factors is required. Third, several clinical parameters, including complications and choice of surgery that can affect red blood cell-related parameters, were not evaluated, which may lead to further selection bias. Finally, the lengthy study period (2003 to 2017) may introduce historical bias.

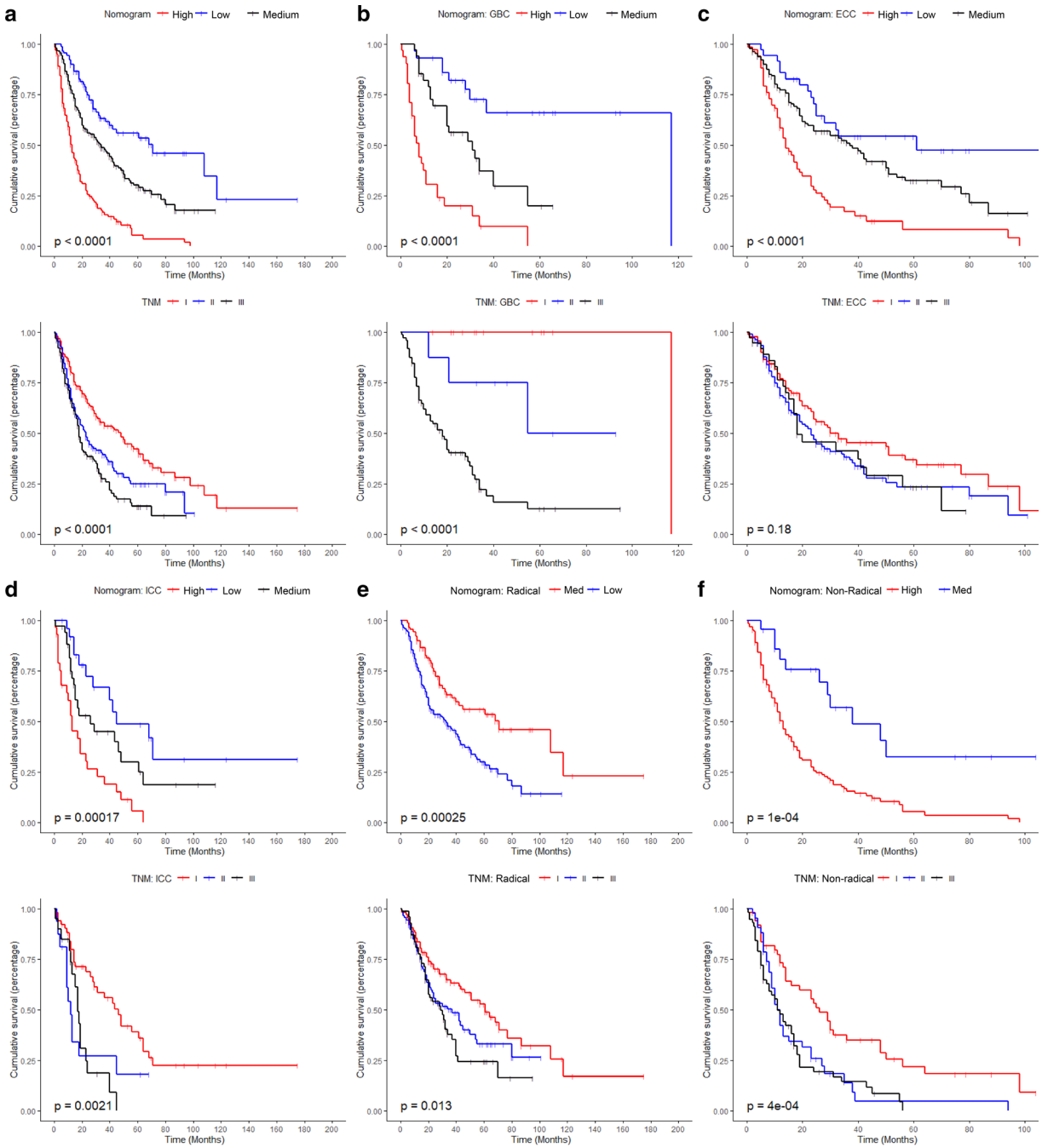


**Fig. 4** Comparison of the TNM staging system with Nomogram A. Kaplan-Meier analysis of OS. **a** Primary cohort. **b** GBC, **c** ECC, **d** ICC, **e** radical resection, and **f** non-radical resection

## CONCLUSION

In conclusion, HALP, which was superior to other red blood cell-related parameters, was identified as an independent prognostic factor for predicting BTC patients' OS. Our nomogram model, based on HALP, TNM, and operative outcome, successfully predicted the probability of survival and revealed advantages compared with the 8th edition of the AJCC TNM system.

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***Compliance with Ethics Guidelines.*** The Medical Ethics Committees of Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College approved the study, which was conducted in accordance with the ethical standards of the World Medical Association's Declaration of Helsinki [18]. The requirement for informed consent was waived because this was a retrospective study.

***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## REFERENCES

1. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet. 2014;383(9935):2168–79.
2. Patel T. Cholangiocarcinoma–controversies and challenges. Nat Rev Gastroenterol Hepatol. 2011;8(4):189–200.
3. Perinel J, Adham M. Preoperative biliary drainage for resectable or borderline resectable periampullary tumor: what is the best management? Hepatob Surg Nutr. 2019;8(4):398–400.
4. Xue L, Guo C, Zhang K, Jiang H, Pang F, Dou Y, et al. Comprehensive molecular profiling of extrahepatic cholangiocarcinoma in Chinese population and potential targets for clinical practice. Hepatob Surg Nutr. 2019;8(6):615–22.
5. Lepage C, Cottet V, Chauvenet M, Phelip JM, Bedenne L, Faivre J, et al. Trends in the incidence and management of biliary tract cancer: a French population-based study. J Hepatol. 2011;54(2):306–10.
6. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz J, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg. 2001;234(5):507–19.
7. Zhang XF, Beal EW, Bagante F, Chakedis J, Weiss M, Popescu I, et al. Early versus late recurrence of intrahepatic cholangiocarcinoma after resection with curative intent. Br J Surg. 2018;105(7):848–56.
8. Ma WJ, Wu ZR, Shrestha A, Yang Q, Hu HJ, Wang JK, et al. Effectiveness of additional resection of the invasive cancer-positive proximal bile duct margin in cases of hilar cholangiocarcinoma. Hepatob Surg Nutr. 2018;7(4):251–69.
9. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93–9.
10. Tang LQ, Li CF, Li J, Chen WH, Chen QY, Yuan LX, et al. Establishment and validation of prognostic nomograms for endemic nasopharyngeal carcinoma. J Natl Cancer Inst. 2016;108(1).

11. Ficarra V, Galfano A, Novara G, Iafrate M, Brunelli M, Secco S, et al. Risk stratification and prognostication of renal cell carcinoma. World J Urol. 2008;26(2):115–25.

12. Yoshida N, Kosumi K, Tokunaga R, Baba Y, Nagai Y, Miyamoto Y, et al. Clinical importance of mean corpuscular volume as a prognostic marker after esophagectomy for esophageal cancer. Ann Surg. 2020;271(3):494–501.

13. Zhang X, Zhang F, Qiao W, Zhang X, Zhao Z, Li M. Low hematocrit is a strong predictor of poor prognosis in lung cancer patients. Biomed Res Int. 2018;2018:6804938.

14. Koma Y, Onishi A, Matsuoka H, Oda N, Yokota N, Matsumoto Y, et al. Increased red blood cell distribution width associates with cancer stage and prognosis in patients with lung cancer. PLoS One. 2013;8(11):e80240.

15. Xu SS, Li S, Xu HX, Li H, Wu CT, Wang WQ, et al. Haemoglobin, albumin, lymphocyte and platelet predicts postoperative survival in pancreatic cancer. World J Gastroenterol. 2020;26(8):828–38.

16. Bozkaya Y, Kurt B, Gurler F. A prognostic parameter in advanced non-small cell lung cancer: the ratio of hemoglobin-to-red cell distribution width. Int J Clin Oncol. 2019;24(7):798–806.

17. J. B, A. L, H. W. Prognostic factors for progression-free and overall survival in advanced biliary tract cancer. Ann Oncol. 2015.

18. Association WM. World medical association declaration of helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–4.

19. Peng D, Zhang CJ, Gong YQ, Hao H, Guan B, Li XS, et al. Prognostic significance of HALP (hemoglobin, albumin, lymphocyte and platelet) in patients with bladder cancer after radical cystectomy. Sci Rep. 2018;8(1):794.

20. Li J, Chen S, Peng S, Liu Y, Xing S, He X, et al. Prognostic nomogram for patients with Nasopharyngeal Carcinoma incorporating hematological biomarkers and clinical characteristics. Int J Biol Sci. 2018;14(5):549–56.

21. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer. 2010;116(18):4256–65.

22. Chakedis J, Spolverato G, Beal EW, Woelfel I, Bagante F, Merath K, et al. Pre-operative sarcopenia identifies patients at risk for poor survival after resection of biliary tract cancers. J Gastrointest Surg. 2018;22(10):1697–708.

23. Jansson H, Cornillet M, Bjorkstrom NK, Sturesson C, Sparrelid E. Prognostic value of preoperative inflammatory markers in resectable biliary tract cancer—validation and comparison of the Glasgow Prognostic Score and Modified Glasgow Prognostic Score in a Western cohort. Eur J Surg Oncol. 2020;46(5):804–10.

24. Cho K-M, Han S-W, Park H, Im S-A, Oh D-Y, Kim T-Y, et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and their dynamic changes during chemotherapy is useful to predict a more accurate prognosis of advanced biliary tract cancer. Oncotarget. 2016;8(2):2329–41

25. Nakashima S, Kobayashi S, Nagano H, Tomokuni A, Tomimaru Y, Asaoka T, et al. BRCA/Fanconi anemia pathway implicates chemoresistance to gemcitabine in biliary tract cancer. Cancer Sci. 2015;106(5):584–91.

26. Alvaro Sanz E, Garrido Siles M, Rey Fernandez L, Villatoro Roldan R, Rueda Dominguez A, Abiles J. Nutritional risk and malnutrition rates at diagnosis of cancer in patients treated in outpatient settings: early intervention protocol. Nutrition. 2019;57:148–53.

27. Yang X-w, Yuan J-m, Chen J-y, Yang J, Gao Q-g, Yan X-z, et al. The prognostic importance of jaundice in surgical resection with curative intent for gallbladder cancer. BMC Cancer. 2014;14.