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Preoperative inflammatory burden index for prognostication in esophageal squamous cell carcinoma undergoing radical resection

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Background The Inflammatory burden Index (IBI) is an effective predictor for a range of malignancies. However, the significance of IBI in esophageal squamous cell carcinoma (ESCC) needs to be further verified. The aim of this study was to verify the predictive power of IBI in ESCC undergoing radical resection.

Methods The current retrospective study, which comprised 408 ESCC patients randomized into either the primary or validation cohort, evaluated the relationships between IBI, clinical characteristics, and cancer-specific survival (CSS). Additionally, the nomogram model was also constructed and verified.

Results The IBI is significantly related to tumor length, vessel invasion, perineural invasion, and TNM stage. Compared to other hematological indices, the decision curve analyses (DCA) and receiver operating characteristic curve (ROC) confirmed the higher prognostic value of IBI, indicating the better clinical applicability. In patients with high IBI compared to the low IBI cohort, the 5-year CSS was considerably worse (total: 27.0% vs. 59.1%, $P < 0.001$; primary: 25.0% vs. 58.9%, $P < 0.001$; validation: 31.7% vs. 59.7%, $P = 0.002$). The IBI was shown to be an independent parameter by multivariate analyses (primary: HR = 2.352, $P < 0.001$; validation: HR = 1.683, $P = 0.045$). Finally, with the C-index of 0.675 (0.656–0.695) in the primary set and 0.662 (0.630–0.694) in the validation set for CSS in ESCC, an IBI-based nomogram was created and validated.

Conclusion The predictive significance of IBI in ESCC patients undergoing radical resection was validated by this investigation. IBI may be utilized for preoperative evaluation of ESCC as it was found to be substantially correlated with prognosis.

Keywords Cancer-specific survival, Recursive partitioning analysis, Inflammatory burden index, Esophageal squamous cell carcinoma, Prognosis

Esophageal cancer (EC), a malignant tumor that is aggressive and poses a major risk to public health, is not uncommon worldwide, including in China[1,2]. One of the main variables influencing the outcomes of EC is the tumor-related pathological stage (TNM stage), which is commonly used to assess the survival[3]. Sometimes, however, the TNM stage alone may not be adequate to determine a patient's prognosis. Therefore, additional indicators may also need to be further investigated. The growing trend of using genetic biomarker detection to determine the EC prognosis is nevertheless constrained by the cost and inconvenience of testing[4,5]. To better improve patient prognosis and inform therapeutic decision-making, it is crucial to more accurately estimate the prognosis of EC prior to treatment using a range of simple, inexpensive, and effective prognostic indicators.

Systemic inflammatory response (SIR), the most representative tumor-host interaction, plays critical roles in cancer progression and prognosis[6,7]. A growing body of research indicates that the prognosis of various malignancies is closely related to a number of hematological indices that represent host SIR, such as albumin (ALB), C-reactive protein (CRP), monocytes (MONs), neutrophils (NEUs), platelets (PLTs), and lymphocytes (LYMs)[8–10]. Additionally, an increasing number of integrative indices with higher sensitivity and specificity are also being developed by researchers based on these SIR-related indices, such as CRP to ALB ratio (CAR),

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systemic immune inflammation index (SII), PLTs to LYMs ratio (PLR), LYMs to MONs ratio (LMR), and NEUs to LYMs ratio (NLR). The outcomes demonstrate that these indices have a higher prognostic role for several malignancies, including EC[11–14]. However, for assessing the prognosis of EC, it is unclear which combination of SIR-related indices is useful. Thus, it is of great clinical significance to explore an indicator that fully reflects the SIR to better predict the prognosis in those with EC.

It has been demonstrated that a novel inflammatory burden index (IBI) that takes SIR into account is a more accurate predictor of cancer[15]. The IBI was created with the intention of helping the authors forecast the prognosis of cancer as well as evaluate the inflammatory burden associated with various malignancies. The IBI's predictive significance has since been verified in a number of cancer cases[16–19]. However, there is a limited understanding of IBI's prognostic significance in patients with EC[20]. Therefore, this study sought to evaluate the prognostic role of preoperative IBI in esophageal squamous cell carcinoma (ESCC) with radical resection. Additionally, a predictive IBI-based nomogram was also constructed and validated to predict individual survival in patients with ESCC.

Materials and methods

Study design and inclusion and exclusion criteria

Retrospective medical records were gathered from 2013 to 2015 for 628 ESCC patients who underwent radical resection. The flow chart of study design and inclusion and exclusion criteria is shown in Fig. 1A. Following a thorough screening process, a total number of 408 cases were finally enrolled and randomly split into either the primary or validation cohort at a ratio of 7:3. The **ethics committee** approved this study and waived the informed consent due to the retrospective nature (IRB.2021-4).

Therapy and follow-up

This study employed surgical procedures such as subtotal minimally invasive or open esophagectomy combined with two-field lymphadenectomy, as reported previously, by the Ivor Lewis or McKeown procedure[21]. Due to the potential impact of neoadjuvant therapy on peripheral indicators, patients undergoing such treatment were not included in the present study. Adjuvant treatment following radical resection in EC was then optional and mostly decided by pathological findings[22,23]. After treatment, patients were checked regularly: first 2 years: every 3 months, next 3 to 5 years: every 6 months, and after 5 years: once a year. Data from this study were last followed up in December 2020.

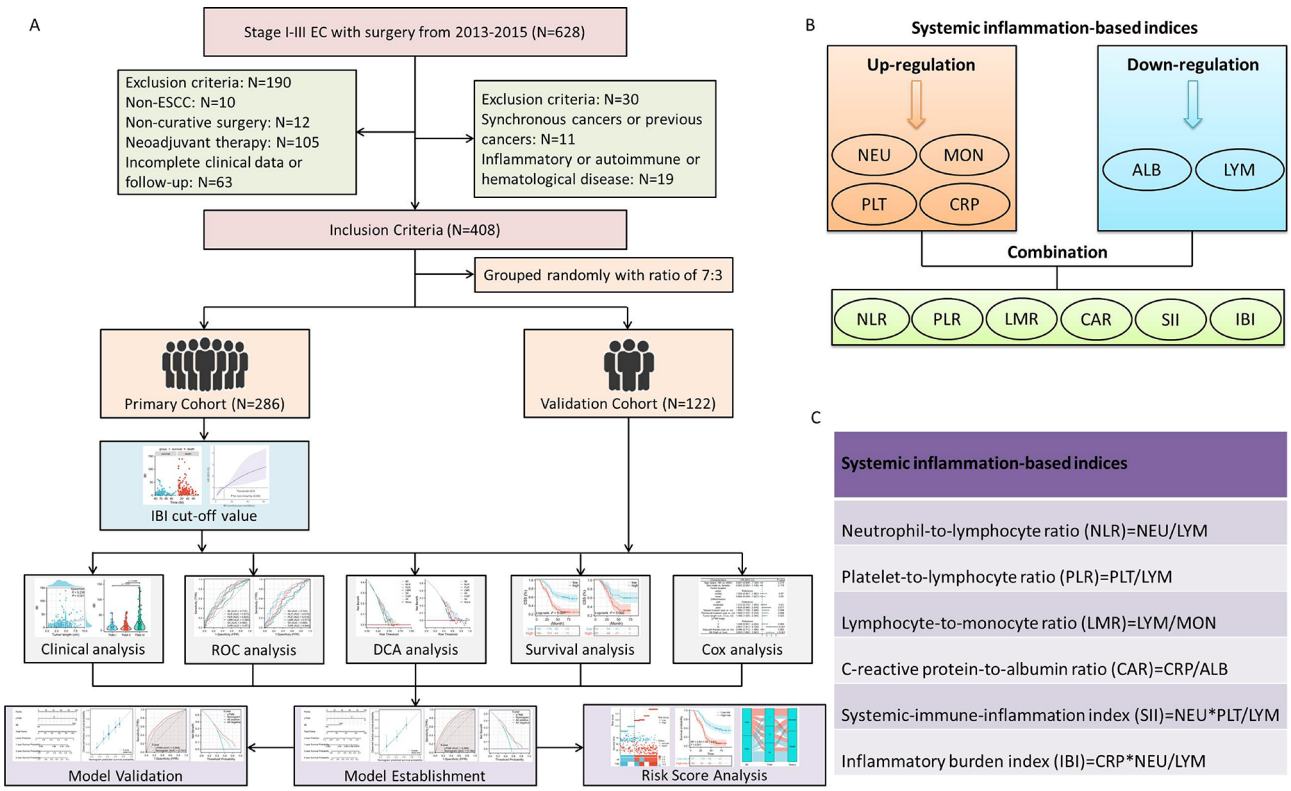

Fig. 1. The flow chart of patient selection and study design (**A**). An overview of the IBI as well as other hematological indices calculation (**B**). The definitions of the integrated hematological indices (**C**).

Laboratory collection and definition

From the medical records, the hematological indices, clinical and demographic features were retrospectively retrieved. In this investigation, the eighth AJCC/UICC TNM classification was used[24]. Preoperative laboratory indicators were gathered a week before surgery. As previously mentioned, the IBI was formulated as CRP × NEU/LYM[15–20]. Figure 1B displays an overview of the IBI as well as other hematological indices calculations. Figure 1C displays the definitions of the integrated hematological indices based on previously published research[11–14].

Statistical analysis

SPSS 20.0, R 4.1.2, and Medcalc 17.6 were used to evaluate the statistical data. Based on the death/survival of cancer-specific survival (CSS), the receiver operating characteristic curve (ROC) was used to compare the areas under the curve (AUCs) between IBI and other indices. A time-independent ROC and AUC verified the IBI's prognostic capabilities. Decision curve analysis (DCA), a tool for assessing the clinical value of various prediction models, was also utilized to analyze the difference between IBI and other hematological indices by measuring net income at various probability thresholds. Using the restricted cubic spline (RCS) model, the appropriate threshold for IBI was obtained by analyzing the non-linear relationship between IBI and CSS. RCS regression uses third-order polynomials joined at knot points to model non-linear relationships, which is highly relevant to Cox regression model analysis. Cox regress analyses were used to identify parameters in CSS that had 95% confidence intervals (CIs) and hazard ratios (HRs). Kaplan-Meier curves were used to compare the variations in CSS. By assessing discrimination and calibration in the primary and validation cohorts, a nomogram model was created and verified. If the P value was less than 0.05, the results were considered statistically significant.

Results

Characteristics comparison between two cohorts

The characteristics as well as hematological indices of the two cohorts were displayed in Table 1 along with a number of hematological indicators. Since there was no discernible difference between the two cohorts, the validation cohort's findings may offer more reliable validation for the primary cohort.

Characteristics grouped by IBI

Figure 2A displays the distribution of all the indices. Figure 2B displays the correlation heat map for the primary cohort. The CSS and IBI exhibited a nonlinear connection (Fig. 2C), thus dividing patients into two separate cohorts after establishing an IBI threshold of 10.6 by RCS (Fig. 2D). Table 2 displays the baseline features and hematological indices sorted by IBI. Individuals exhibiting elevated IBI had longer tumor length, more vessel and perineural invasion, and a more advanced TNM stage. Figure 2E displays a positive correlation between IBI and tumor length. Patients with a high level of IBI were also found to have a considerably greater tumor stage (Fig. 2F) and death risk (Fig. 2G), according to the violin plots.

Prognostic comparison between IBI and other indices

DCAs and ROCs between IBI and other traditional indices (SII, CAR, PLR, NLR, and LMR) were conducted in order to have a better understanding of the predictive utility of IBI. The DCAs supported the higher prognostic value of IBI in comparison to other hematological indices, indicating the IBI's potential for improved clinical

	Total ($n=408$)	Primary cohort ($n=286$)	Validation cohort ($n=122$)	*P*-value
Age (mean ± SD, years)	59.6 ± 7.7	59.2 ± 8.0	60.5 ± 7.1	0.125
Sex (female/male, n, %)	132(32.4)/276(67.6)	93(32.5)/193(67.5)	39(32.0)/83(68.0)	0.913
Tumor location (U/M/L, n, %)	26(6.4)/191(46.8)/191(46.8)	18(6.3)/129(45.1)/139(48.6)	8(6.6)/62(50.8)/52(42.6)	0.533
Differentiation (W/M/P, n, %)	63(15.4)/264(64.7)/81(19.9)	40(14.0)/189(66.1)/57(19.9)	23(18.9)/75(61.5)/24(19.8)	0.450
Vessel invasion (yes/no, n, %)	67(16.4)/341(83.6)	47(16.4)/239(83.6)	20(16.4)/102(83.6)	0.992
Perineural invasion (yes/no, n, %)	78(19.1)/330(80.9)	58(20.3)/228(79.7)	20(16.4)/102(83.6)	0.361
Tumor length (mean ± SD, cm)	4.03 ± 1.80	4.05 ± 1.87	3.99 ± 1.64	0.786
pTNM stage (I/II/III, n, %)	137(33.6)/131(32.1)/140(34.3)	95(33.2)/90(31.5)/101(35.3)	42(34.4)/41(33.6)/39(32.0)	0.803
Adjuvant therapy (yes/no, n, %)	119(29.2)/289(70.8)	84(29.4)/202(70.6)	35(28.7)/87(71.3)	0.890
NEU (mean ± SD, 10^9/L)	4.36 ± 1.41	4.41 ± 1.53	4.24 ± 1.07	0.246
LYM (mean ± SD, 10^9/L)	1.57 ± 0.47	1.59 ± 0.49	1.54 ± 0.40	0.383
MON (mean ± SD, 10^9/L)	0.51 ± 0.18	0.52 ± 0.18	0.49 ± 0.16	0.139
PLT (mean ± SD, 10^9/L)	220.9 ± 67.2	217.8 ± 68.9	228.1 ± 62.7	0.158
ALB (mean ± SD, d/dL)	4.09 ± 0.43	4.07 ± 0.46	4.15 ± 0.34	0.081
CRP (mean ± SD, mg/L)	5.34 ± 5.60	5.52 ± 6.08	4.93 ± 4.27	0.327
NLR (mean ± SD, range)	2.90 ± 0.98	2.93 ± 1.09	2.82 ± 0.65	0.276
PLR (mean ± SD, range)	150.3 ± 59.8	148.1 ± 61.1	155.6 ± 56.6	0.245
LMR (mean ± SD, range)	3.26 ± 0.94	3.22 ± 0.89	3.36 ± 1.03	0.167
CAR (mean ± SD, range)	1.33 ± 1.43	1.39 ± 1.58	1.20 ± 1.04	0.221
SII (mean ± SD, range)	648.1 ± 305.4	648.2 ± 327.8	647.9 ± 246.3	0.993
IBI (mean ± SD, range)	15.9 ± 19.2	16.7 ± 21.2	14.2 ± 13.5	0.224

Table 1. Clinical characteristics of ESCC patients in the primary and validation cohorts. **Abbreviation**: ESCC: esophageal squamous cell carcinoma; SD: standard deviation; U/M/L: upper/middle/lower; W/M/P; well/moderate/poor; pTNM: pathological tumor node metastasis; NEU: neutrophil; LYM: lymphocyte; MON: monocyte; PLT: platelet; ALB: albumin; CRP: c-reactive protein; NLR: NEU to LYM ratio; PLR: PLT to LYM ratio; LMR: LYM to MON ratio; CAR: CRP to ALB ratio; SII: systemic immune-inflammation index; IBI: inflammatory burden index.

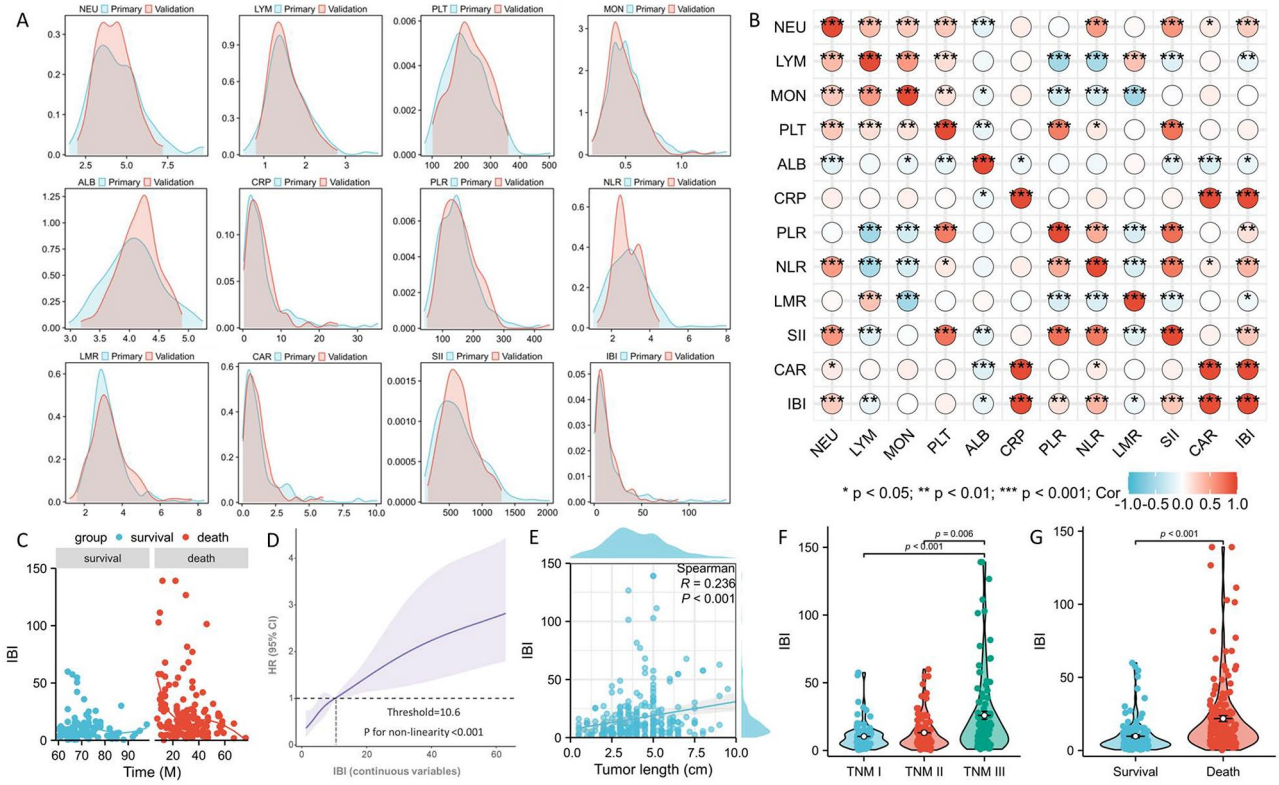

Fig. 2. The distribution of all the indices in two cohorts (**A**). The correlation heat map for all SIR-related indices (**B**). A nonlinear connection between CSS and IBI (**C**). An IBI threshold of 10.6 by RCS (**D**). A positive correlation between IBI and tumor length (**E**). IBI grouped by tumor stage (**F**) and death risk (**G**).

	Primary Cohort ($n=286$) **Low-IBI ($n=146$) High-IBI ($n=140$) P-value**	**Validation Cohort ($n=122$)** **Low-IBI ($n=62$) High-IBI ($n=60$) P-value**
Age (≤60/>60, years, n)	77(52.7)/69(47.3) 92(65.7)/48(34.3) 0.026	34(54.8)/28(45.2) 32(53.3)/28(46.7) 0.868
Sex (female/male, n)	46(31.5)/100(68.5) 47(33.6)/93(66.4) 0.709	22(35.5)/40(64.5) 17(28.3)/43(71.3) 0.397
Tumor location (U/M/L, n)	10(6.8)/60(41.1)/76(52.1) 8(5.7)/69(49.3)/63(45.0) 0.379	4(6.5)/25(40.3)/33(53.2) 4(6.7)/37(61.7)/19(31.6) 0.048
Differentiation (W/M/P, n)	24(16.4)/94(64.4)/28(19.2) 16(11.4)/95(67.9)/29(20.7) 0.473	12(19.4)/36(58.1)/14(22.5) 11(18.3)/39(65.0)/10(16.7) 0.671
Vessel invasion (yes/no, n)	16(11.0)/130(89.0) 31(22.1)/109(77.9) 0.011	5(8.1)/57(91.9) 15(25.0)/45(75.0) 0.012
Perineural invasion (yes/no, n)	20(13.7)/126(86.3) 38(27.1)/102(72.9) 0.005	6(9.7)/56(90.3) 14(23.3)/46(76.7) 0.042
Tumor length (≤3.0/>3.0, n)	65(44.5)/81(55.5) 35(25.0)/105(75.0) 0.001	26(41.9)/36(58.1) 15(25.0)/45(75.0) 0.048
pTNM stage (I/II/III, n)	57(39.0)/52(35.6)/37(25.3) 38(27.1)/38(27.1)/64(45.8) 0.001	28(45.2)/18(29.0)/16(25.8) 14(23.4)/23(38.3)/23(38.3) 0.039
Adjuvant therapy (yes/no, n)	40(27.4)/106(72.6) 44(31.4)/96(68.6) 0.454	42(67.7)/20(32.3) 45(75.0)/15(25.0) 0.376

Table 2. Clinical characteristics grouped by IBI in the primary and validation cohorts. **Abbreviation**: ESCC: esophageal squamous cell carcinoma; IBI: inflammatory burden index; U/M/L: upper/middle/lower; W/M/P; well/moderate/poor; pTNM: pathological tumor node metastasis.

application (Fig. 3A-B). When compared to other traditional indices, IBI exhibited the greatest AUC based on the ROCs, suggesting a stronger predictive capacity (Fig. 3D-F). In order to better represent the prognostic value of IBI, we further adopted time-dependent ROC curves (Fig. 4A-C) and AUC curves (Fig. 4D-F). Compared to other hematological indices, the results also showed the prognostic advantages of IBI (Fig. 4G-L).

Kaplan-Meier curves of CSS and Cox analysis

In patients with high IBI compared to the low IBI cohort, the 5-year CSS was considerably worse (total: 27.0% vs. 59.1%, $P<0.001$, Fig. 5A; primary: 25.0% vs. 58.9%, $P<0.001$, Fig. 5B; validation: 31.7% vs. 59.7%, $P=0.002$, Fig. 5C). Prominent prognostic variables from the univariate analyses with regard to CSS, including TNM stage, perineural and vessel invasion, tumor length, and IBI were then recruited for further multivariate analyses in the primary cohort (Fig. 5D). IBI was shown to be an independent parameter in the primary cohort (HR = 2.352, $P<0.001$; Fig. 5E). The similar results of IBI in Cox analyses were also obtained in the validation cohort (HR = 1.683, $P=0.045$; Fig. 5F-G).

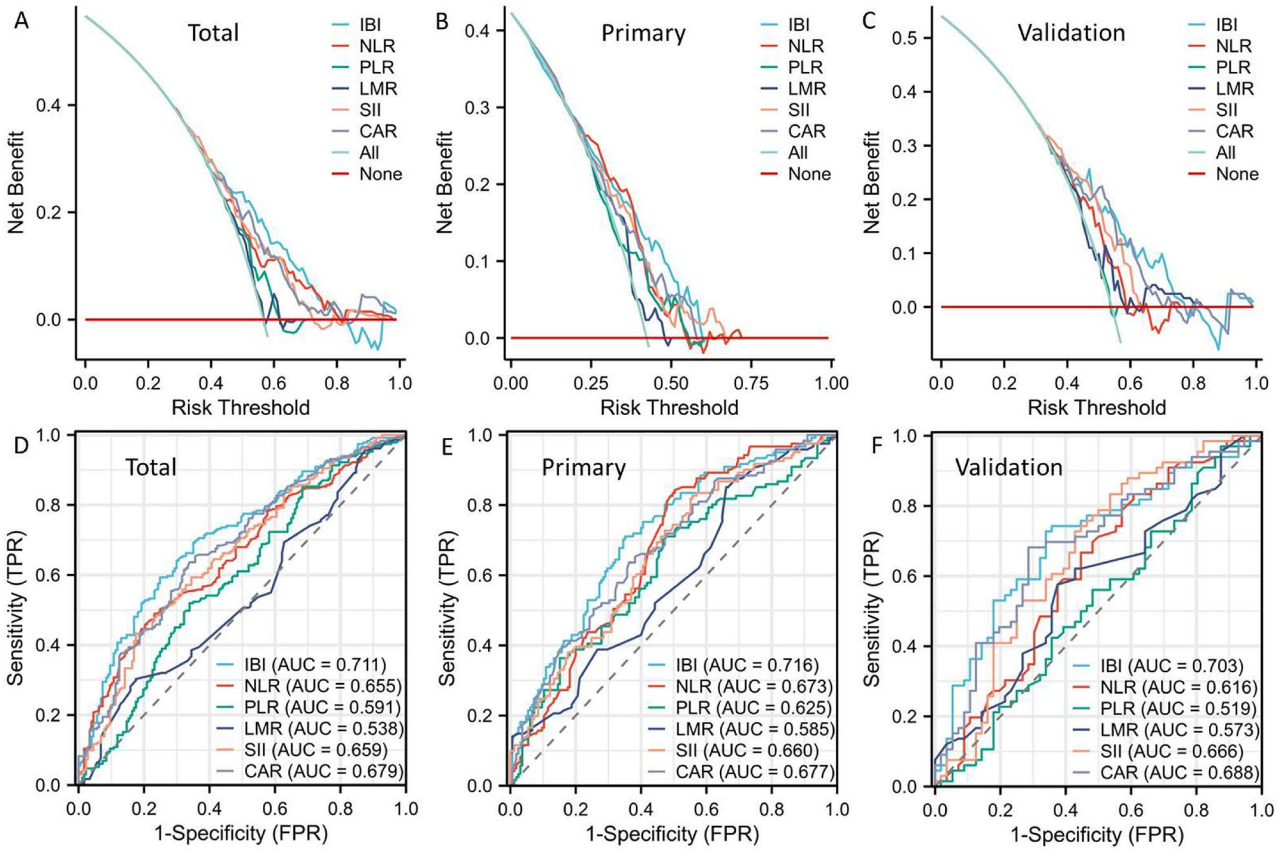

Fig. 3. To better understand the prognostic value of IBI, DCAs (**A**-**C**) and ROCs (**D**-**F**) between IBI and other conventional indices were compared.

Nomogram establishment and validation

To forecast 1-, 3-, and 5-year CSS, two predictive nomograms made up of two independent parameters (TNM stage and IBI) were created and validated in the primary and validation cohorts, respectively (Fig. 6A-B). The C-indexes for CSS were 0.675 (0.656–0.695) and 0.662 (0.630–0.694) in the primary and validation cohorts, respectively. Compared to two cohorts of the individual 5-year CSS, the results showed satisfactory levels of agreement (Fig. 6C-D). The nomogram had better prediction of 5-year CSS on account of the ROCs (Fig. 6E-F) and DCAs (Fig. 6G-J). The nomogram model was used as the foundation for risk stratification, dividing the population into high-risk and low-risk categories (Fig. 7A-B). There was a noticeable variation in CSS between the two risk categories, as seen in Fig. 7C-D. The Sankey diagram in respect to risk stratification is shown in Fig. 7E-F.

Discussion

To stratify patients, at present, optimize treatments, and forecast survival in ESCC, the TNM stage is the most widely utilized tool[3]. Nevertheless, one drawback of the TNM stage mentioned above is that it only takes into account the features of cancer, excluding host factors like SIR that could have an impact on the prognosis of the disease[25]. A growing body of research indicates that the prognosis for EC has been predicted and validated using a number of SIR-related factors[10,13,14]. Consequently, future prognostic improvement will be guided by more improved and composite SIR-related indices. The predictive impact of IBI was validated in this investigation, and it was found to be much stronger than that of other traditional prognostic indices. Compared with patients in the low IBI set, this study also revealed a worse CSS in patients with high IBI. IBI then functions as an independent parameter in two cohorts.

Tumor-related inflammation is strongly associated with tumor occurrence, development, invasion, and metastasis because it is widely thought to be the immune system's reaction to tumor cells[6,7]. The SIR, the most representative tumor-host interaction, is thought to be a hallmark of tumors, which can remarkably accelerate tumor growth by changing the tumor microenvironment, which in turn affects stromal cell renewal rate and polarized immune cell immunosuppressive capacity[26,27]. As markers of tumor aggressiveness and treatment response, SIR-related indices can help customize therapeutic approaches because they show the relationship between the tumor microenvironment and the host immune response[28].

The IBI, one of the most creative and promising prognostic indices, thoroughly assesses inflammatory burden in cancer patients. In a prospective multicenter research involving 6359 cancer patients, the first thorough

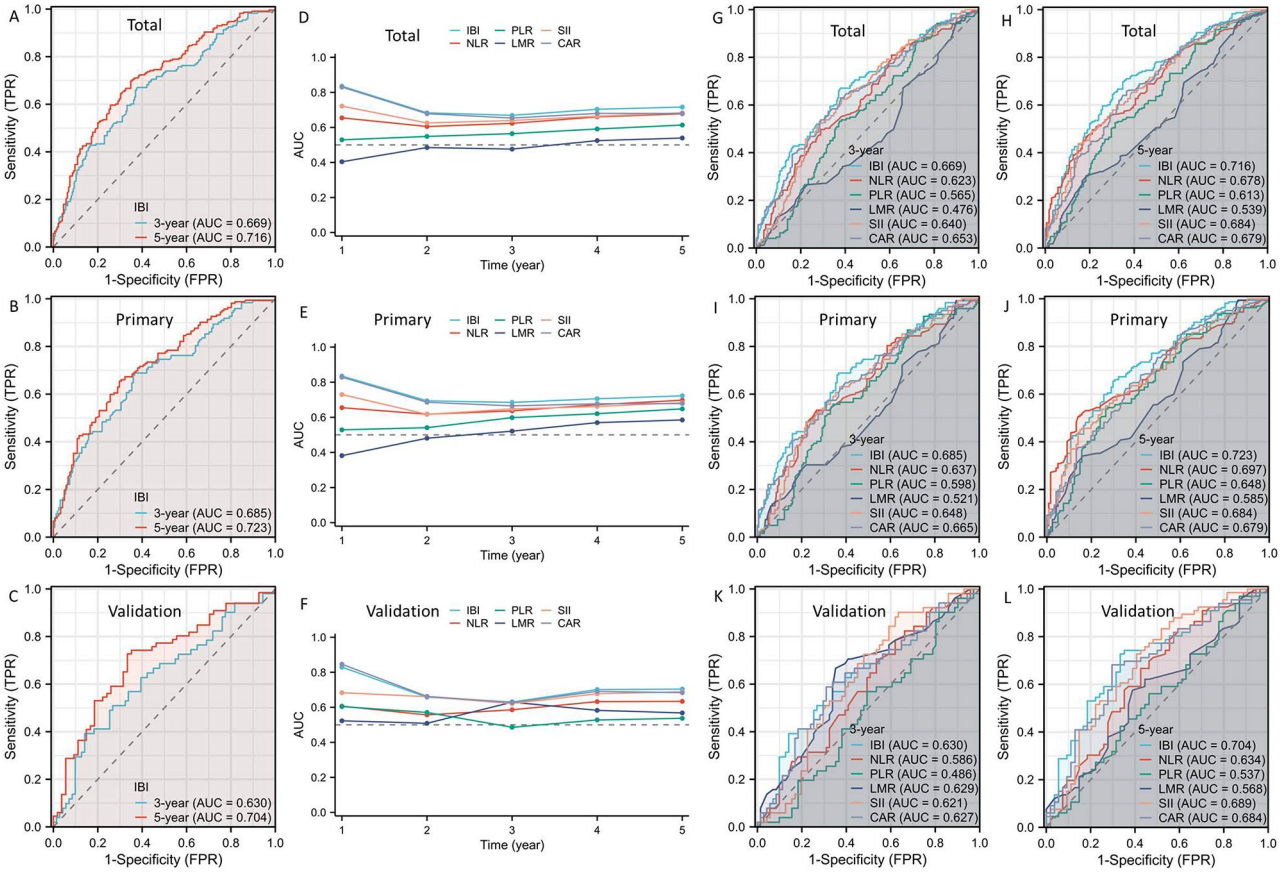

Fig. 4. Time-dependent ROC curves (**A**-**C**) and AUC curves (**D**-**F**). The results also showed the prognostic advantages of IBI (**G**-**L**).

examination of IBI was presented and indicated that IBI was an independent high-risk variable associated with short-term outcomes, nutritional status, and life functions[15]. In response to the above study, researchers had noted that the lack of external validation of IBI was not conducive to clinical application. Therefore, they proved that IBI was of great significance to the prognosis through external verification in locally advanced gastric cancer, and therefore believe that IBI will provide a more personalized reference for prognostic monitoring[16]. Based on the findings of a study including 93 gastric cancer patients who had multimodal therapy, a high IBI was linked to an increasing risk of death and postoperative complications[17]. A multicenter prospective study aimed to compare the prognostic value of existing SIR-related indices in non-small cell lung cancer patients, suggesting that a high level of IBI was linked to a high incidence of cachexia, death risk, and 90-day complications[18]. Additionally, IBI was also found to be able to predict a poor prognosis in a research involving 701 patients who had hepatocellular carcinoma resection[19].

Nevertheless, there haven't been many pertinent results of IBI in ESCC. Furthermore, the superiority of IBI over its constituents and other traditional indices in predicting the prognosis of ESCC remains unclear. Recently, a study analyzed the associations between IBI and prognosis in EC[20]. Between the current study and the prior study, there were a few discrepancies. First of all, the preceding study included a range of EC forms and treatments, and these intricate variables might have an impact on the result. Secondly, this study's results were created in the primary set and validated in the validation set, correspondingly, and its samples were larger than those of the previous study. Thirdly, no additional conventional indices were included in the prior study for comparison. In order to ascertain the IBI's superiority in the present investigation, prognostic values were compared between the IBI and additional classical indices. Notably, IBI demonstrated the highest predictive power and clinical application on account of ROCs and DCAs, making it the best option for SIR-related prognostic stratification in ESCC. Fourthly, the hematological indices listed above may not be the same for other cancers because ESCC has unique characteristics and its patients are typically malnourished. Finally, the current study constructed and validated a predictive nomogram for survival prediction based on IBI. The findings of our study shed new light on the prognostic importance of IBI in ESCC.

With the inclusion of three crucial parameters–LYMs, NEUs, and CRP–the IBI has become a useful instrument for evaluating the intricacy of the inflammatory process. By releasing a variety of pro-inflammatory cytokines, CRP can induce SIR and ultimately cause the death of cancer patients by slowly depleting vital protein components in the host[29]. Research has additionally revealed a strong association between CRP, cancer stage, and inflammatory response[30]. NEUs have a pro-tumor effect by attracting immune-suppressive cells to the

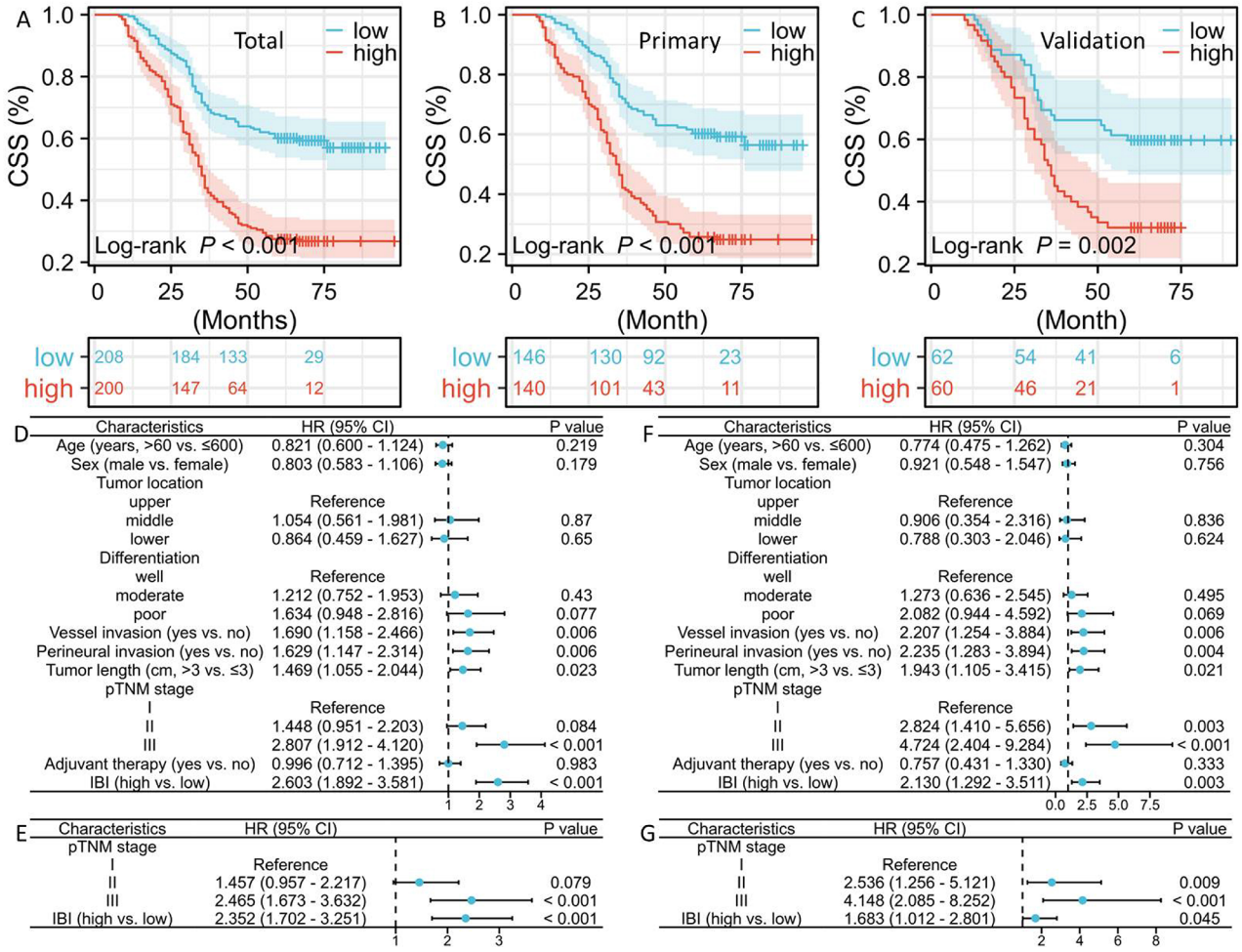

Fig. 5. The 5-year CSS in total (**A**), primary (**B**), and validation (**C**) cohort. Univariate (**D**) and multivariate (**E**) Cox analyses in the primary cohort. Univariate (**F**) and multivariate (**G**) Cox analyses in the validation cohort.

tumor microenvironment[31]. Additionally, by releasing extracellular traps through cytotoxic lymphocyte release, tumor-associated NEUs shield tumor cells from toxic death, hence encouraging tumor angiogenesis[32]. Likely to impair the growth and invasion of tumor cells, LYMs can penetrate the tumor microenvironment, which is why they are frequently employed as an indicator of immunological competence[33]. As an efficient defense against tumor cells, LYMs, on the other hand, play a part in immune regulation within the tumor microenvironment[34]. The IBI is linked to both SIR status and tumor-related variables, suggesting that it is a more reliable prognostic indicator than other traditional indices. This should make it easier for supervising clinicians to use IBI to make preliminary assessments of patients' clinical status and to focus more on probable complications and early hospitalization prognoses[35,36].

It is important to recognize a few of this study's strengths. First of all, the findings verified that individuals with ESCC who had higher baseline values of IBI also had higher tumor stages and poorer prognoses. Secondly, the superiority was ascertained by comparing the prognostic values of IBI with other traditional indices. Interestingly, IBI demonstrated the best predictive capability in terms of CSS among all the most often used SIR-related indices. Thirdly, the great predictive accuracy and low cost and convenience of calculating the IBI from regular laboratory tests suggest that it will likely be highly useful in ESCC daily clinical practice. Fourthly, it is hypothesized that IBI could reduce potential biases and improve the utility of prognosis. IBI is more accurate and has greater clinical relevance when compared to other hematological indices. Adjuvant therapy may be necessary for patients in an advanced stage, and greater monitoring may be necessary for those in an earlier stage.

Currently, there are a large number of studies on imaging and minimal residual disease (MRD) in cancer prediction. Radiomics is a non-invasive technology that involves extracting quantitative features from medical pictures, selecting features using specific procedures, and analyzing correlations with clinical data for classification or prediction[37]. In EC, radiomics has been shown to better predict pathological reactions such as pathological full response, complications, recurrence, and prognosis[38,39]. MRD refers to the small amount of cancer cells that remain in the body following cancer treatment. These remaining cancer cells have either failed to respond or are

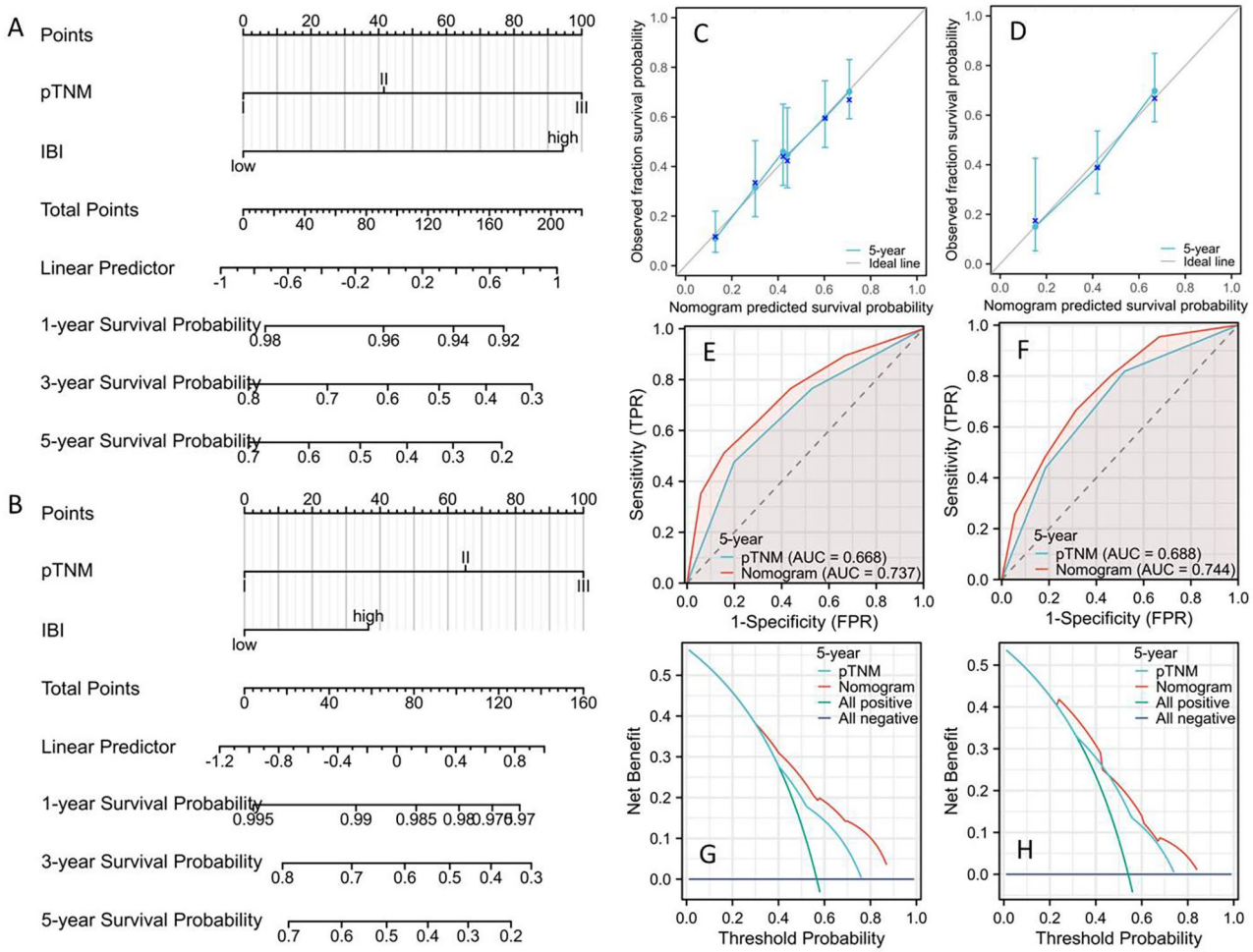

Fig. 6. Nomograms in primary (**A**) and validation (**B**) cohort. The CCAs showed satisfactory levels of agreements in the primary (**C**) and validation cohort (**D**). The ROCs indicated a higher prognostic ability in the primary (**E**) and validation cohort (**F**). The DCAs displayed a better clinical applicability in the primary (**G**) and validation cohort (**H**).

resistant to treatment[40]. Some studies have looked into the role of ctDNA-based MRD surveillance in the early treatment and prognosis of EC[41,42]. MRD is currently a hot research topic, but it has not been fully promoted due to its price and technology. Therefore, more clinical study findings are needed to determine whether MRD may be used as a prognostic predictor of EC.

It is important to take into account some of the study's limitations. To begin with, potential bias was unavoidable in this single-center retrospective research. Secondly, IBI, a useful and straightforward index obtained from peripheral blood, might be impacted in different status, restricting the application. Thirdly, the fact that individuals who underwent neoadjuvant therapy were not included in this study may have limited the findings. Therefore, additional perspective studies are required to demonstrate the predictive validity of IBI.

Conclusion

In summary, in patients with ESCC who underwent radical resection, IBI was verified as a useful and straightforward index. Preoperative evaluation may benefit from the relationship between IBI and the tumor's stage and prognosis.

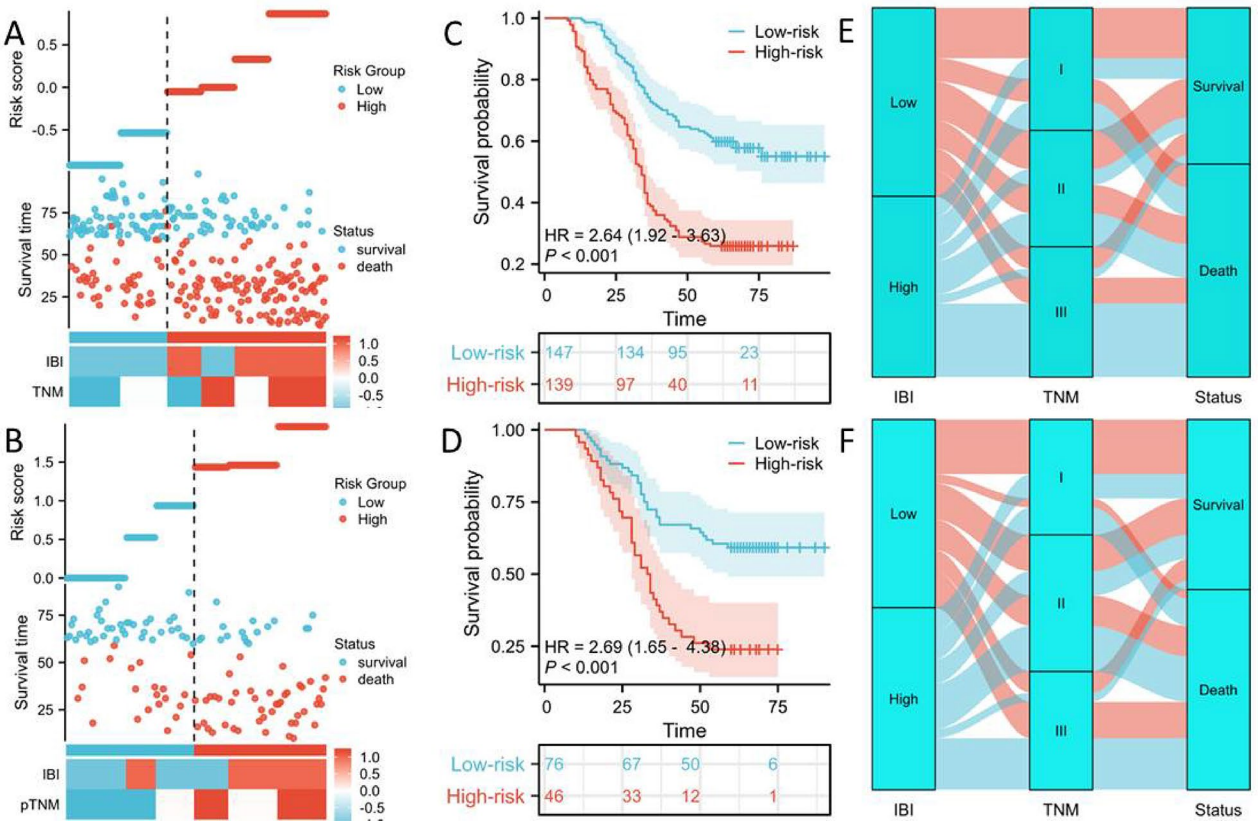

Fig. 7. Risk was categorized into high-risk and low-risk groups in the primary (**A**) and validation cohort (**B**). The 5-year CSS between the two groups in the primary (**C**) and validation cohort (**D**). Sankey diagram with relation to risk stratification in the primary (**E**) and validation cohort (**F**).

Data availability

All data are available upon request. Further inquiries can be directed to the corresponding author.

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Author contributions

JF and QC contributed and designed the current study. QZ, LW, and JF drafted the manuscript. LW and XY contributed to data collect. JF and YX interpreted and analyzed the data. JF and QC reviewed the manuscript for important intellectual content critically. All authors contributed to the article and approved the final manuscript as submitted version.

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Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of Zhejiang Cancer Hospital (IRB-2021-4).

Conflict of interest

The authors declare no conflict of interests.

Additional information

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