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Preoperative immune prognostic index predicts the prognosis and postoperative adjuvant chemotherapy benefits of esophageal squamous cell carcinoma after minimally invasive esophagectomy

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Abstract

Background The utility of the immune prognostic index (IPI) for esophageal squamous cell carcinoma (ESCC) has yet to be established after minimally invasive esophagectomy (MIE). The purpose of this study was to investigate the value of IPI in predicting the prognosis and postoperative adjuvant chemotherapy (AC) benefits of ESCC patients.

Methods Between January 2011 and December 2018, 613 ESCC patients underwent MIE at our center and were divided into two groups: low IPI and high IPI**.**Log-rank tests were used to compare the overall survival (OS) and disease-free survival (DFS) of patients in different groups based on Kaplan–Meier survival analysis. Differences in clinical characteristics between groups were eliminated by propensity score matching (PSM) analysis. To identify independent risk factors influencing OS and DFS, the Cox proportional risk model was used.

Results In comparison to the high IPI group, the low IPI group had a better 5-year OS and DFS in both the entire and matched cohorts ($P<0.05$). IPI was found to be an independent prognostic factor for OS and DFS in a multivariate analysis of the entire cohort and the matched cohort ($P<0.05$). In subgroup analyses of most clinicopathological factors, high IPI was associated with a higher risk of death or recurrence in the matched cohorts. When combined with 8th TNM staging, the 5-year OS and DFS of stage II or III patients with low IPI in the AC group were not different from those in the non-AC group ($P>0.05$), and AC of stage III patients with high IPI significantly prolonged 5-year OS and DFS (OS: 37.4% vs 26.2%, $P=0.018$; DFS: 33.6% vs 19.8%, $P=0.042$).

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Conclusion Preoperative IPI is a promising predictor of ESCC after MIE. For stage III ESCC patients with high IPI, AC can significantly reduce the risk of death or recurrence.

Keywords Esophageal squamous cell carcinoma, Minimally invasive esophagectomy, IPI, Adjuvant chemotherapy benefit

Background

The most common type of esophageal cancer in Asia is esophageal squamous cell carcinoma (ESCC), which accounts for approximately 90% of all cases [1, 2]. Radical surgery is the preferred treatment for ESCC, and minimally invasive esophagectomy (MIE) is less invasive and has a better prognosis than open esophagectomy (OE), which has been widely used worldwide [3, 4]. Despite significant advances in postoperative multidisciplinary treatment (chemotherapy and radiotherapy), patients with ESCC have a poor prognosis, with a 5-year overall survival rate of less than 50% [5, 6]. As a result, an effective indicator that can predict ESCC patients'future survival and determine the benefit of postoperative adjuvant therapy is critical for developing individualized treatment options in advance and improving patient survival.

Recent studies have found that tumor immune escape is one of the main mechanisms leading to cancer progression and that the immune inflammatory reaction plays an important role in it [7–9]. A number of blood inflammatory response indicators, such as platelet-to-lymphocyte ratio (PLR), derived neutrophil-to-lymphocyte ratio (dNLR), lymphocyte-to-monocyte ratio (LMR), and serum lactate dehydrogenase (LDH), are linked to a poor prognosis in many types of cancer patients (gastric cancer, esophageal cancer, lung cancer, etc.) [10–14]. However, a single index is ineffective in predicting cancer patients'long-term survival. As a result, some researchers developed an immune prognostic index (IPI) that combines dNLR and LDH to identify cancer patient populations with a higher chance of survival [15, 16]. To date, the predictive value of IPI for primary ESCC after MIE has not been reported.

Some previous studies have found that patients with locally advanced ESCC who undergo surgery only without neoadjuvant induction therapy may benefit from postoperative adjuvant chemotherapy (AC) [17, 18]. In contrast, other studies have shown that AC after surgery does not improve survival [19, 20]. This could be because chemotherapy not only increases the immune response or makes cancer cells more susceptible to immune attack, but it also causes bone marrow suppression and immune cell depletion, resulting in immune suppression [21, 22]. The tumor-node-metastasis (TNM) staging is widely used in patients who are clearly receiving chemotherapy [23]. However, the benefit of AC varies between individuals of the same stage, so additional metrics in conjunction with the TNM stage to identify patients who will benefit from AC are urgently needed [24].

Therefore, in this study, we attempted to establish the immune prognostic index (IPI) of esophageal cancer after MIE using dNLR and LDH, explore the effect of IPI on the long-term oncology outcome of ESCC patients, and analyze the AC benefit population.

Materials and methods

Ethics statement

This study followed the Helsinki Declaration protocols and was approved by the Institutional Review Board of Fujian Medical University Union Hospital (IRB number: 2021HX003). The requirement for written informed consent was waived by the ethics committee of Fujian Medical University Union Hospital because of the retrospective nature of the study.

Study population

In our study, patients with ESCC treated at Fujian Medical University Union Hospital between January 2011 and December 2018 were enrolled. Inclusion criteria included the following: (1) Patients diagnosed with ESCC and receiving MIE; (2) Complete clinicopathological information; (3) No invasion to the surrounding organs or metastasis; and (4) Negative postoperative pathological margin (R0). Exclusion criteria included the following: (1) Patients received OE; (2) Preoperative neoadjuvant chemoradiotherapy; (3) Death within 30 days of the operation; and (4) Incomplete records of clinicopathological information or loss of follow-up. In total, 613 patients with ESCC were enrolled in the study (Fig.S1).

Treatment protocol

In the McKeown procedure, the patient is initially positioned in the left lateral decubitus position, with access achieved via a right thoracic incision. After ligating the azygos vein, the periesophageal tissue is meticulously dissected, and the left and right recurrent laryngeal nerves, as well as the subcarinal and lower mediastinal lymph nodes, are carefully identified and excised. The patient is then repositioned to the supine position for abdominal access. Tissue dissection is performed with precision, preserving the right side of the gastric arc, and the left gastric artery, common hepatic artery, splenic lymph

nodes, and surrounding tissue are resected. A 4-cm-wide gastric conduit is fashioned using a linear stapler. Finally, a manual or mechanical cervical esophagogastric anastomosis is performed on the left side of the neck [25]. For the Ivor Lewis procedure, after separating the stomach and dissecting the abdominal lymph nodes through an upper abdominal incision, a gastric conduit is created. Next, the esophagus is separated, and the thoracic lymph nodes are dissected through a right thoracotomy. Finally, the gastric conduit is lifted through the esophageal bed, and the proximal esophagus and gastric conduit are anastomosed in the right chest [26]. Two-field lymphadenectomy was routinely performed in patients with middle and lower thoracic esophageal cancer, while three-field lymphadenectomy was performed in patients with upper thoracic esophageal cancer.

In our study, adjuvant therapy is primarily recommended for patients with pT1-4aN + M0 and pT4aN0M0 stages of esophageal squamous cell carcinoma. For patients with pT1-T3 N0M0 stage, observation is recommended, while T4aN0M0 patients may either be observed or receive adjuvant therapy, depending on specific circumstances. The indications for adjuvant therapy are based on postoperative pathological results, the patient's overall health status, and treatment preferences, and are typically assessed through a multidisciplinary consultation [27–29]. The main postoperative adjuvant chemotherapy regimens include platinum-based therapy combined with paclitaxel or docetaxel, administered every three weeks. The common adjuvant chemotherapy regimens are as follows:Cisplatin (60 mg/m^2) on day 1, followed by albumin-bound paclitaxel (125 mg/m^2) on days 1 and 8;Alternatively, docetaxel (75 mg/m^2) on day 1 and cisplatin (60 mg/m^2) on day 1 [20].In clinical practice, the doses may be adjusted according to the patient's tolerance, especially for elderly patients or those who experience adverse reactions. During the treatment course, patient responses are closely monitored, and adjustments are made as necessary.

Definition

All patients underwent MIE, either McKeown minimally invasive esophagectomy (McKeown-MIE) or Ivor Lewis minimally invasive esophagectomy (Ivor Lewis-MIE). Lymph node dissection included two- or three-field lymph node dissection.

According to the 8th American Joint Committee on Cancer (AJCC) staging system, we recommend that patients with stage II/III ESCC receive platinum-based adjuvant chemotherapy (fluorouracil plus platinum, docetaxel plus platinum, or paclitaxel plus platinum). Patients who received postoperative adjuvant chemotherapy (AC) after completing at least one cycle of adjuvant chemotherapy were distinguished from those who did not receive postoperative adjuvant chemotherapy (AC) (Non-AC).

Blood samples were collected from all ESCC patients 7 days before surgery, and the white blood cell count, neutrophil count, and LDH concentration were measured. The dNLR was defined as absolute neutrophil count/(white blood cell concentration-absolute neutrophil count). According to the analysis results of X-tile software, the cut-off values for dNLR and LDH for the best prediction of OS were 1.70 and 197.0 IU/L, respectively (Fig.S2 A–F), and the same results were obtained for the best cut-off values of DFS (Fig.S3 A–F). IPI was calculated based on the dichotomous values of dNLR (< 1.70 was considered as low dNLR, score 0; ≥ 1.70 was high dNLR, score 1) and LDH (< 197.0 IU/L was considered as low LDH, score 0; ≥ 197.0 IU/L was high LDH, score 1), and then, the whole population was divided into two groups according to the IPI score: a low IPI group with a score of 0 and a high IPI group with a score of 1 or 2.

Follow-up

Patients were followed up in the clinic or by telephone. The patients were followed up every 3 months for 1 year after surgery, every 6 months until 5 years after surgery, and once a year after 5 years. Patients were followed up until death or until a cut-off date in December 2019. A patient's overall survival (OS) was determined by the number of days from surgery until death from any cause or the end of the last follow-up period. A disease-free time (DFS) is defined as the time interval between radical surgery and tumor metastasis, recurrence, or death.

Statistical analysis

Based on historical data [30], Compared to IPI 0, LIPI 1 and 2 had a HR of 1.419 (95% CI: 1.063–1.895, P= 0.018) and 2.064(95% CI: 1.403–3.036, P< 0.001). Using a log-rank test with 90% power and a two-sided alpha of 0.05, An additional 10% was added for loss to follow-up, resulting in a total sample of 420. Categorical variables between the two groups were analyzed by $\chi 2$ test or Fisher's exact test, while continuous variables were presented as mean ± standard and subjected to t-test or Mann–Whitney U test. Significant differences between the two groups (excluding dNLR and LDH included in IPI) were eliminated using a propensity score matching (PSM) method. The X-tile (Version 3.6.1) was used to calculate the best cut-off of dNLR and LDH, which were divided into low dNLR or high dNLR and low LDH or high LDH, respectively. The area under the curve (AUC) of the receiver operating characteristic curve (ROC) was used to compare the ability of dNLR, LDH and IPI, to predict

the prognosis of patients. A Kaplan–Meier method was used to calculate OS and DFS before and after matching, and the log-rank test was used to determine the survival difference between the two groups. Univariate and multivariate analyses were performed using Cox regression models to identify independent risk factors affecting ESCC patients.

All tests were two-sided and statistically significant with a $P < 0.05$ setting. SPSS version 26.0 and R language version 3.6.3 were used for statistical analysis in the study.

Results

Clinicopathological information of the entire cohort and matched cohort

Our study included 613 ESCC patients, including 407 (66.4%) male patients and 206 (33.6%) female patients who received MIE. In the upper, middle, and lower thoracic segments, 56 (9.1%), 395 (64.4%), and 162 (26.4%) tumors were located, respectively. The tumor histologic grade was G2 in 281 (45.8%) of the patients and G3 in 76. There were 166 (27.1%) patients in the T1 stage, 114 (18.6%) patients in the T2 stage, and 333 (54.3%) patients in the T3/T4a stage. There were 309 (50.4%) patients who received adjuvant chemotherapy after the operation and 304 (49.6%) patients who did not receive adjuvant chemotherapy after the operation. The mean preoperative dNLR and LDH of the included patients were 1.62 ± 0.90 and (175.2 ± 41.7) IU/L, respectively (Table 1).

Among the low IPI group, there were 311 patients (50.7%), while among the high IPI group, there were 302 patients (49.3%). We found that there were significant differences in the histologic grade, T stage, Clavien–Dindo grade, LDH (IU/L), and dNLR between the two groups ($P < 0.05$). Therefore, we performed a PSM to balance the basic information between the two groups. In the matched cohort, 261 (46.4%) patients were in the low IPI group and 302 (53.6%) patients were in the high IPI group. All clinicopathological information was eliminated in the matched cohort.

Survival analysis in the entire cohort

Kaplan–Meier survival results showed that the 5-year OS of low and high dNLR was 68.5% and 48.1%, and the 5-year DFS was 62.9% and 44.2%, respectively (All $P < 0.001$) (Fig. 1A,B). The 5-year OS of low LDH and high LDH was 66.4% and 43.9%, and the 5-year DFS was 60.5% and 41.5%, respectively (All $P < 0.001$) (Fig. 1C,D). The 5-year OS of low IPI and high IPI was 71.9% and 50.2%, and the 5-year DFS was 65.7% and 46.4%, respectively (All $P < 0.001$) (Fig. 1E,F). In order to further compare the predictive ability of the three indicators, ROC analysis was performed in the entire cohort, and the AUC of preoperative IPI for predicting 3- and 5-year OS was 0.614 (95%CI 0.567–0.660) and 0.607 (95%CI 0.550–0.665), respectively. The AUC of 3- and 5-year DFS was 0.592 (95%CI 0.545–0.638) and 0.587 (95%CI 0.529–0.646), respectively. Compared with the prediction ability of dNLR and LDH, IPI had the largest AUC in predicting 3- and 5-year OS and 3- and 5-year DFS (Fig.S4 A–D).

Prognostic value of IPI in the entire cohort

Cox univariate analysis showed that age, T-stage, histologic grade, N-stage, intraoperative bleeding, Clavien–Dindo grade, LDH, dNLR, and IPI were risk factors for OS (All $P < 0.05$). Multivariate analysis showed that IPI (High vs. Low: HR 1.880; 95% CI 1.327–2.665; $P < 0.001$), T-stage (T3/4 A vs. T1: HR 2.906; 95% CI 1.722–4.902; $P < 0.001$), N-stage (N1 vs. N0: HR 2.138; 95% CI 1.468–3.113; $P < 0.001$; N2/3 vs. N0: HR 3.207; 95% CI 2.219–4.637; $P < 0.001$), intraoperative bleeding (≥ 200 vs. ≤ 100: HR 2.122; 95% CI 1.375–3.275; $P = 0.001$), and Clavien–Dindo grade (≥ II vs. < II: HR 1.430; 95% CI 1.072–1.907; $P = 0.015$) were independent risk factors for OS. Similarly, in addition to the T-stage, Clavien–Dindo grade, N-stage, and intraoperative bleeding (All $P < 0.05$), IPI (HR 1.657; 95% CI 1.212–2.266; $P = 0.002$) was also an independent prognostic index for DFS (Table 2).

Survival analysis in the matching cohort

After matching, Kaplan–Meier analysis showed that the 5-year OS of low and high dNLR was 67.8% and 48.1% and the 5-year DFS was 62.4% and 44.2%, respectively (All $P < 0.001$) (Fig. 2A,B). The 5-year OS of low LDH and high LDH was 65.6% and 43.9% and the 5-year DFS was 59.7% and 46.4% (All $P < 0.001$), respectively (Fig. 2C,D). The 5-year OS of low IPI and high IPI was 71.3% and 50.2% and the 5-year DFS of high IPI and low IPI was 65.0% and 46.4%, respectively (All $P < 0.001$) (Fig. 2E,F). We further used the ROC curve to compare the predictive ability of the three indexes. In the matched cohort, the AUC of preoperative IPI for predicting 3- and 5-year OS was 0.619 (95%CI 0.572–0.666) and 0.616 (95%CI 0.558–0.673), respectively. The AUC of 3- and 5-year DFS was 0.594 (95%CI 0.548–0.641) and 0.598 (95%CI 0.540–0.656), respectively. These AUC values suggest that IPI has a moderate ability to predict long-term survival outcomes, with values between 0.6 and 0.7 generally considered as indicating moderate discriminative power.

Similarly, when compared to dNLR and LDH, IPI showed the highest AUC values in predicting both OS and DFS at 3 and 5 years, indicating that it performs better than the other two markers in distinguishing between patients with different survival outcomes. The AUC of

Table 1 Patient characteristics in the entire and matched cohort

Characteristics	Entire cohort				Propensity score-matched cohort			
	Total($N = 613$)	Low IPI ($N = 311$)	High IPI ($N = 302$)	*P*-value	Total($N = 563$)	Low IPI ($N = 261$)	High IPI ($N = 302$)	*P*-value
Age(years)				0.166				0.157
≤ 65	487(79.4%)	254(81.7%)	233(77.2%)		447(79.4%)	214(82.0%)	233(77.2%)	
> 65	126(20.6%)	57(18.3%)	69(22.8%)		116(20.6%)	47(18.0%)	69(22.8%)	
Sex				0.548				0.217
Female	206(33.6%)	101(32.5%)	105(34.8%)		183(32.5%)	78(29.9%)	105(34.8%)	
Male	407(66.4%)	210(67.5%)	197(65.2%)		380(67.5%)	183(70.1%)	197(65.2%)	
BMI (kg/m2)				0.98				0.826
≤ 18.5	65(10.6%)	33(10.6%)	32(10.6%)		56(9.9%)	24(9.2%)	32(10.6%)	
18.5–25	461(75.2%)	233(74.9%)	228(75.5%)		426(75.7%)	198(75.9%)	228(75.5%)	
≥ 25	87(14.2%)	45(14.5%)	42(13.9%)		81(14.4%)	39(14.9%)	42(13.9%)	
Tumor location				0.796				0.537
Proximal	56(9.1%)	26(8.4%)	30(9.9%)		49(8.7%)	19(7.3%)	30(9.9%)	
Mid	395(64.4%)	202(65.0%)	193(63.9%)		365(64.8%)	172(65.9%)	193(63.9%)	
Distal	162(26.4%)	83(26.7%)	79(26.2%)		149(26.5%)	70(26.8%)	79(26.2%)	
Histologic grade				0.038				0.279
Gx/G1	256(41.8%)	120(38.6%)	136(45.0%)		244(43.3%)	108(41.4%)	136(45.0%)	
G2	281(45.8%)	158(50.8%)	123(40.7%)		246(43.7%)	123(47.1%)	123(40.7%)	
G3	76(12.4%)	33(10.6%)	43(14.2%)		73(13.0%)	30(11.5%)	43(14.2%)	
T stage				0.026				0.618
T1	166(27.1%)	98(31.5%)	68(22.5%)		136(24.2%)	68(26.1%)	68(22.5%)	
T2	114(18.6%)	59(19.0%)	55(18.2%)		101(17.9%)	46(17.6%)	55(18.2%)	
T3/T4a	333(54.3%)	154(49.5%)	179(59.3%)		326(57.9%)	147(56.3%)	179(59.3%)	
N stage				0.052				0.163
N0	326(53.2%)	170(54.7%)	156(51.7%)		292(51.9%)	136(52.1%)	156(51.7%)	
N1	149(24.3%)	83(26.7%)	66(21.9%)		137(24.3%)	71(27.2%)	66(21.9%)	
N2/3	138(22.5%)	58(18.6%)	80(26.5%)		134(23.8%)	54(20.7%)	80(26.5%)	
TNM stage				0.324				0.871
I	167(27.2%)	93(29.9%)	74(24.5%)		142(25.2%)	68(26.1%)	74(24.5%)	
II	180(29.4%)	88(28.3%)	92(30.5%)		167(29.7%)	75(28.7%)	92(30.5%)	
III/IVA	266(43.4%)	130(41.8%)	136(45.0%)		254(45.1%)	118(45.2%)	136(45.0%)	
Surgical procedure				0.679				0.383
McKeown	551(89.9%)	278(89.4%)	273(90.4%)		503(89.3%)	230(88.1%)	273(90.4%)	
Ivor Lewis	62(10.1%)	33(10.6%)	29(9.6%)		60(10.7%)	31(11.9%)	29(9.6%)	
Lymphadenectomy				0.695				0.905
Two-field	553(90.2%)	282(90.7%)	271(89.7%)		506(89.9%)	235(90.0%)	271(89.7%)	
Three-field	60(9.8%)	29(9.3%)	31(10.3%)		57(10.1%)	26(10.0%)	31(10.3%)	
Intraoperative bleeding(ml)				0.555				0.286
≤ 100	318(51.9%)	164(52.7%)	154(51.0%)		293(52.0%)	139(53.3%)	154(51.0%)	
100–200	211(34.4%)	109(35.0%)	102(33.8%)		196(34.8%)	94(36.0%)	102(33.8%)	
≥ 200	84(13.7%)	38(12.2%)	46(15.2%)		74(13.1%)	28(10.7%)	46(15.2%)	
Clavien–Dindo grade				0.028				0.1
< II	342(55.8%)	187(60.1%)	155(51.3%)		307(54.5%)	152(58.2%)	155(51.3%)	
≥ II	271(44.2%)	124(39.9%)	147(48.7%)		256(45.5%)	109(41.8%)	147(48.7%)	
Adjuvant chemotherapy				0.97				0.674
No	304(49.6%)	154(49.5%)	150(49.7%)		275(48.8%)	125(47.9%)	150(49.7%)	
Yes	309(50.4%)	157(50.5%)	152(50.3%)		288(51.2%)	136(52.1%)	152(50.3%)	
LDH(IU/L)				< 0.001				< 0.001

Table 1 (continued)

Characteristics	Entire cohort				Propensity score-matched cohort			
	Total($N = 613$)	Low IPI ($N = 311$)	High IPI ($N = 302$)	*P*-value	Total($N = 563$)	Low IPI ($N = 261$)	High IPI ($N = 302$)	*P*-value
Mean ± SD	175.9 ± 41.5	158.5 ± 20.7	193.9 ± 49.4		177.1 ± 42.8	157.7 ± 21.1	193.9 ± 49.3	
dNLR				< 0.001				< 0.001
Mean ± SD	1.62 ± 0.90	1.19 ± 0.29	2.06 ± 1.09		1.67 ± 0.92	1.21 ± 0.29	2.06 ± 1.09	

IPI for predicting 3- and 5-year OS (0.619 and 0.616) and 3- and 5-year DFS (0.594 and 0.598) is higher than that of dNLR and LDH, which typically suggests that IPI is a more reliable predictor in this cohort.

The ROC curves are shown in Fig.S6 A, B, C, and D, which further illustrate the performance of IPI, dNLR, and LDH in predicting OS and DFS at 3 and 5 years.

Prognostic value of IPI in the matched cohort

Using matched cohorts, a Cox proportional hazards regression analysis was performed. Similar to that before matching, age, T-stage, histologic grade, intraoperative bleeding, N-stage, Clavien–Dindo grade, LDH, dNLR, and IPI were risk factors for OS (All $P < 0.05$). Multivariate Cox analysis found that IPI (High vs. Low: HR 1.886; 95% CI 1.323–2.689; $P < 0.001$), T-stage (T3/4 A vs. T1: HR 2.832; 95% CI 1.657–4.843; $P < 0.001$), N-stage (N1 vs. N0: HR 2.071; 95% CI 1.414–3.033; $P < 0.001$; N2/3 vs. N0: HR 3.097; 95% CI 2.135–4.492; $P < 0.001$), intraoperative bleeding (≥ 200 vs. ≤100: HR 2.244; 95% CI 1.452 −3.469; $P < 0.001$), and Clavien–Dindo grade (≥ II vs. < II: HR 1.373; 95% CI 1.026–1.837; $P = 0.015$) were independent risk factors for OS. In terms of DFS, IPI (HR 1.500; 95% CI 1.121 −2.009; $P = 0.006$) was still an independent prognostic factor (Table 3).

We conducted an additional subgroup analysis on the matched cohort to evaluate IPI's predictive ability on each clinicopathological factor. It was found that in most subgroups, the OS (Fig. 3) and DFS (Fig. 4) of the low IPI group were superior to those of the high IPI group, and IPI could also effectively predict the long-term prognosis of patients in subgroup analysis.

Predicting AC benefits for stage II/III ESCC patients with IPI based on matched cohort data

In the matched cohort, AC affected OS ($P < 0.05$) but not DFS ($P > 0.05$) in stage II/III patients. According to a stratified analysis, AC did not prolong OS or DFS in stage II patients ($P > 0.05$). However, in stage III patients, AC not only affected OS but also DFS ($P < 0.05$) (Fig.S6 A–F). Therefore, AC is beneficial in stage III patients.

We further investigated the role of IPI in AC by Kaplan–Meier analysis. In the low IPI group, AC did not affect OS and DFS in stage II or III patients (All $P > 0.05$) (Fig. 5A–F). In the high IPI group, AC did not change the prognosis of stage II patients ($P > 0.05$). However, in stage III patients, AC prolonged 5-year OS and DFS (OS: 37.4% vs 26.2%, $P = 0.018$; DFS: 33.6% vs 19.8%, $P = 0.042$) (Fig. 6A–F). Thus, our study shows that stage III patients in the high IPI group may benefit from AC.

Discussion

Increasing evidence suggests that in addition to the traditional pathological TNM stage, tumor differentiation, and tumor burden, the immunoinflammatory status is associated with the prognosis of cancer patients after radical surgery [31–33]. Current studies have shown that the inflammatory process is a mechanism by which cancer cells produce immune resistance, promote tumor angiogenesis, invasion, and proliferation, and activate oncogenic signaling pathways [34, 35]. Furthermore, preoperative peripheral inflammatory indicators such as NLR, LMR, PLR, and SIS can reflect the immune inflammatory status of the tumor's living environment and are used to predict long-term oncology outcomes in cancer patients [12, 13, 36]

In recent years, preoperatively dNLR has been widely used in many cancers, including gastric cancer, esophageal cancer, and renal cancer, as an index covering monocytes and other granulocyte subsets, providing comparable or better predictive value than NLR [37–39]. LDH is an enzyme that promotes anaerobic glycolysis and is associated with the immune inflammatory environment of tumor hypoxia [40]. Based on the combination of dNLR and LDH, Mezquita et al. proposed a new biomarker of circulating inflammation called the immune prognostic index (IPI). Lung cancer patients with high IPI status have a poor prognosis when treated with immune checkpoint inhibitors (ICIs), and IPI can be used as a

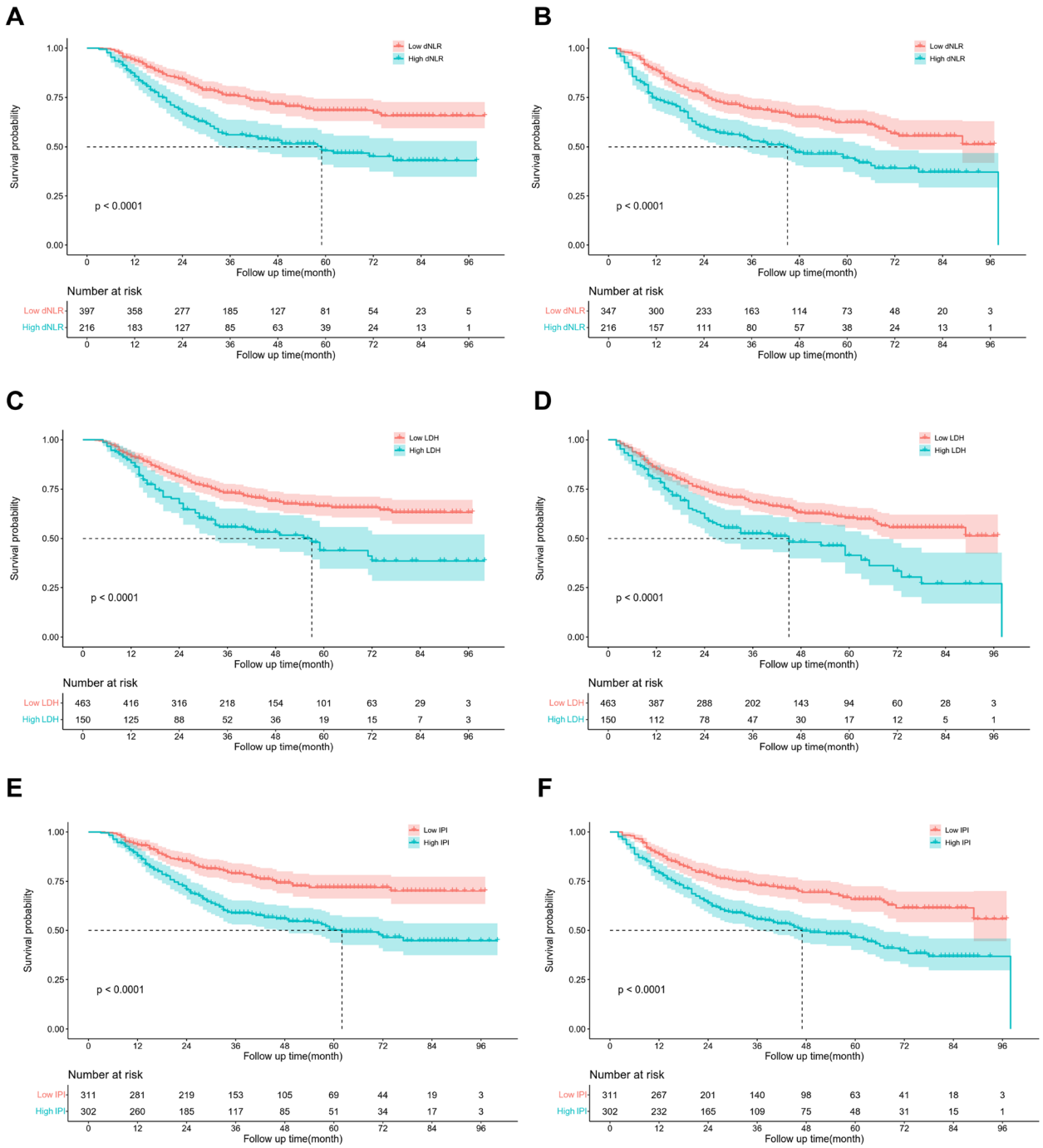

Fig. 1 Kaplan–Meier analyses of OS according to the (**A**) dNLR、(**C**) LDH and (**E**) IPI group; Kaplan–Meier analyses of DFS according to the (**B**) dNLR, (**D**) LDH and (**F**) IPI group in the entire cohort

marker to identify those who would benefit from ICIs [15]. Feng et al. reported that IPI is an independent index affecting cancer-specific survival (CSS) of ESCC patients after surgery, and it is also significantly correlated with CSS in the subgroup analysis of TNM staging [41]. However, in the era of minimally invasive treatment, whether IPI can predict the survival of ESCC is not clear, and the relationship between IPI and AC benefit has not been studied.

In different studies, the threshold values of dNLR and LDH are different. Previous studies have found that IPI formed by the combination of preoperative dNLR (> 3.0)

Table 2 Univariate and multivariate analysis for overall survival and disease -free survival in the entire cohort

Characteristics	Overall survival				Disease-free survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR with 95%CI	*P*-value	HR with 95%CI	*P*-value	HR with 95%CI	*P*-value	HR with 95%CI	*P*-value
Age(years)								
≤ 65								
> 65	1.526(1.106–2.106)	0.01	1.374(0.987–1.913)	0.06	1.395(1.032–1.885)	0.03	1.232(0.890–1.704)	0.208
Sex								
Female								
Male	0.950(0.691–1.306)	0.751			0.830(0.617–1.116)	0.218		
BMI (kg/m2)								
≤ 18.5								
18.5–25	0.997(0.627–1.563)	0.991			1.154(0.746–1.783)	0.52		
≥ 25	1.112(0.641–1.928)	0.706			1.382(0.823–2.320)	0.221		
Tumor location								
Proximal								
Mid	1.169(0.695–1.967)	0.556			1.366(0.828–2.254)	0.222		
Distal	1.235(0.706–2.160)	0.46			1.330(0.777–2.276)	0.299		
Histologic grade								
Gx/G1								
G2	1.144(0.842–1.553)	0.389	1.263(0.921–1.733)	0.147				
G3	1.601(1.044–2.457)	0.031	1.421(0.921–2.195)	0.113				
T stage								
T1								
T2	2.420(1.353–4.327)	0.003	1.775(0.978–3.220)	0.059	2.206(1.345–3.615)	0.002	1.732(1.036–2.898)	0.036
T3/T4a	4.869(2.983–7.946)	< 0.001	2.906(1.722–4.902)	< 0.001	3.951(2.613–5.975)	< 0.001	2.590(1.647–4.072)	< 0.001
N stage								
N0								
N1	2.456(1.706–3.536)	< 0.001	2.138(1.468–3.113)	< 0.001	2.093(1.504–2.911)	< 0.001	1.906(1.342–2.708)	< 0.001
N2/3	4.113(2.934–5.767)	< 0.001	3.207(2.219–4.637)	< 0.001	3.735(2.757–5.058)	< 0.001	3.170(2.259–4.448)	< 0.001
Surgical procedure								
McKeown								
Ivor Lewis	0.731(0.455–1.175)	0.196			0.817(0.539–1.239)	0.817		
Lymphadenectomy								
Two-field								
Three-field	1.031(0.666–1.596)	0.89			0.953(0.628–1.447)	0.822		
Intraoperative bleeding(ml)								
≤ 100								
100–200	1.231(0.906–1.674)	0.184	1.149(0.843–1.567)	0.38	1.146(0.862–1.524)	0.349	1.136(0.853–1.514)	0.383
≥ 200	1.998(1.313–3.041)	0.001	2.122(1.375–3.275)	0.001	2.156(1.492–3.115)	< 0.001	2.285(1.562–3.341)	< 0.001
Clavien–Dindo grade								
< II								
≥ II	1.796(1.354–2.383)	< 0.001	1.430(1.072–1.907)	0.015	1.750(1.351–2.266)	< 0.001	1.388(1.064–1.810)	0.016
Adjuvant chemotherapy								
No								
Yes	1.326(0.998–1.762)	0.052			1.392(1.073–1.807)	0.013	0.861(0.642–1.152)	0.313
LDH(IU/L)								
Mean ± SD	1.004(1.002–1.007)	0.001	1.003(1.000–1.006)	0.074	1.003(1.001–1.006)	0.005	1.002(0.999–1.005)	0.12
dNLR								
Mean ± SD	1.150(1.035–1.279)	0.009	0.906(0.769–1.069)	0.243	1.122(1.014–1.240)	0.025	0.894(0.768–1.041)	0.894
IPI group								
Low								
High	2.106(1.570–2.825)	< 0.001	1.880(1.327–2.665)	< 0.001	1.892(1.452–2.465)	< 0.001	1.657(1.212–2.266)	0.002

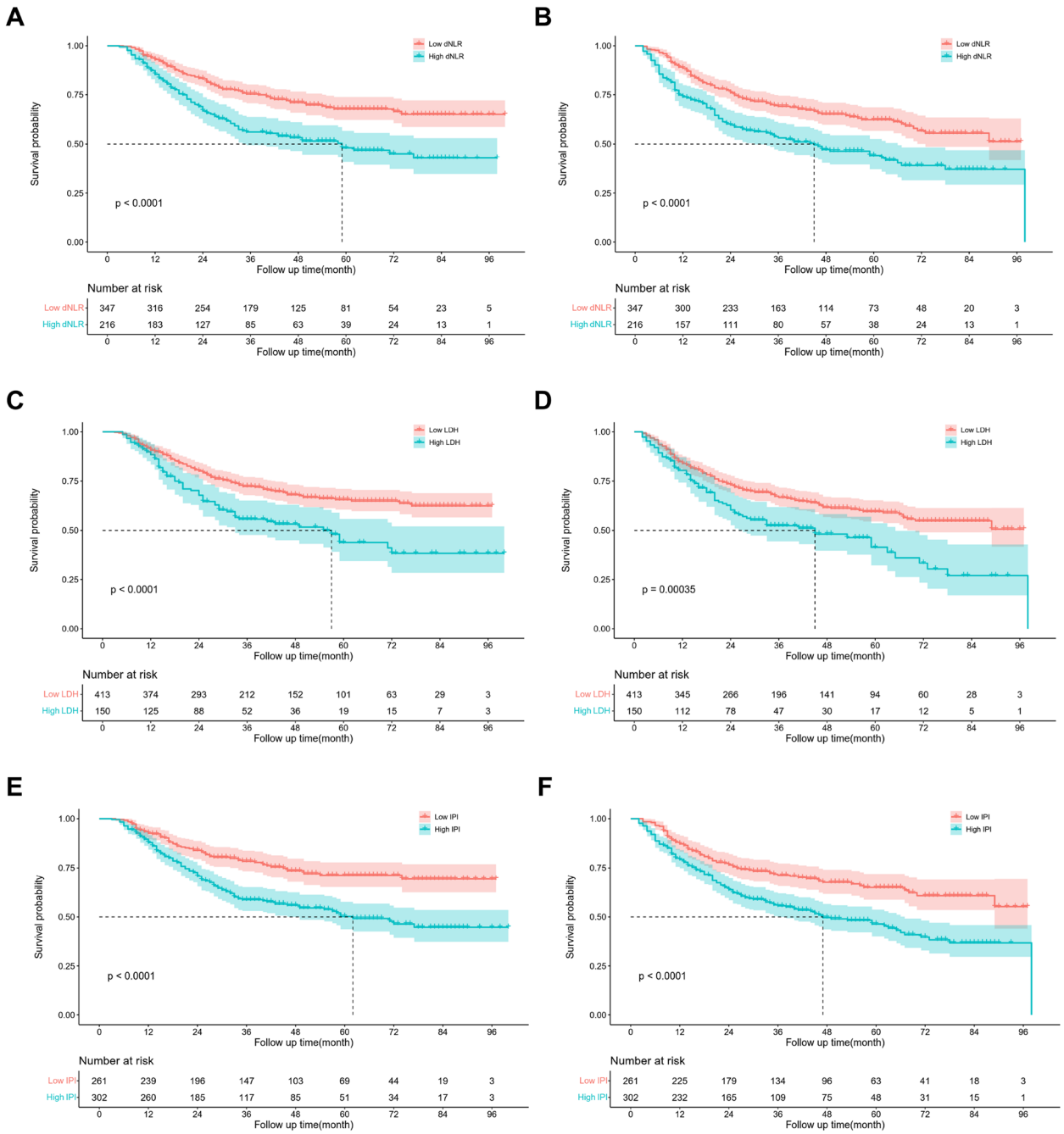

Fig. 2 Kaplan–Meier analyses of OS according to the (**A**) dNLR, (**C**) LDH and (**E**) IPI group; Kaplan–Meier analyses of DFS according to the (**B**) dNLR, (**D**) LDH and (**F**) IPI group in the PSM cohort

and LDH (> 240U/L) is a potential predictor of ESCC after radical resection [41]. In addition, the thresholds for dNLR and LDH were set to 1.97 and 191 IU/L in Yu et al.'s study of locally advanced non-surgical ESCC [42]. X-tile software can classify the biomarkers related to prognosis and survival data into the best cut-off value, which is widely used in clinical oncology research [43]. In this study, we used X-tile software to obtain the best cut-off values of dNLR and LDH for predicting OS and DFS as 1.7 and 190 IU/L, respectively (Fig.S2 and S3). According to the results of the cut-off values, we established the IPI scoring system based on dNLR and LDH, which

Table 3 Univariate and multivariate analysis for overall survival and disease -free survival in the matched cohort

Characteristics	Overall survival				Disease-free survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR with 95%CI	*P*-value	HR with 95%CI	*P*-value	HR with 95%CI	*P*-value	HR with 95%CI	*P*-value
Age(years)								
≤ 65								
> 65	1.517(1.096–2.101)	0.012	1.388(0.993–1.938)	0.055	1.394(1.029–1.890)	0.032	1.233(0.890–1.708)	0.208
Sex								
Female								
Male	0.967(0.701–1.334)	0.838			0.854(0.633–1.151)	0.3		
BMI (kg/m2)								
≤ 18.5								
18.5–25	1.148(0.703–1.874)	0.582			1.316(0.819–2.115)	0.257		
≥ 25	1.277(0.712–2.291)	0.412			1.585(0.913–2.751)	0.101		
Tumor location								
Proximal								
Mid	1.281(0.737–2.226)	0.38			1.479(0.870–2.514)	0.148		
Distal	1.347(0.747–2.431)	0.322			1.442(0.819–2.539)	0.205		
Histologic grade								
Gx/G1								
G2	1.166(0.855–1.589)	0.331	1.227(0.891–1.690)	0.21	1.145(0.865–1.516)	0.344		
G3	1.623(1.058–2.491)	0.027	1.414(0.915–2.185)	0.119	1.344(0.895–2.018)	0.154		
T stage								
T1								
T2	2.172(1.189–3.970)	0.012	1.661(0.894–3.084)	0.108	1.928(1.157–3.213)	0.012	1.523(0.895–2.592)	0.121
T3/T4a	4.492(2.717–7.428)	< 0.001	2.832(1.657–4.843)	< 0.001	3.552(2.332–5.411)	< 0.001	2.399(1.513–3.804)	< 0.001
N stage								
N0								
N1	2.372(1.639–3.431)	< 0.001	2.071(1.414–3.033)	< 0.001	2.045(1.463–2.859)	< 0.001	1.828(1.282–2.607)	0.001
N2/3	3.864(2.745–5.438)	< 0.001	3.097(2.135–4.492)	< 0.001	3.523(2.591–4.791)	< 0.001	2.947(2.103–4.131)	< 0.001
Surgical procedure								
McKeown								
Ivor Lewis	0.686(0.422–1.116)	0.129			0.772(0.505–1.179)	0.231		
Lymphadenectomy								
Two-field								
Three-field	0.969(0.620–1.513)	0.889			0.898(0.587–1.375)	0.621		
Intraoperative bleeding(ml)								
≤ 100								
100–200	1.199(0.878–1.637)	0.255	1.154(0.842–1.581)	0.373	1.118(0.837–1.492)	0.45	1.151(0.861–1.540)	0.343
≥ 200	2.106(1.382–3.209)	0.001	2.244(1.452–3.469)	< 0.001	2.241(1.544–3.253)	< 0.001	2.398(1.631–3.526)	< 0.001
Clavien–Dindo grade								
< II								
≥ II	1.679(1.261–2.235)	< 0.001	1.373(1.026–1.837)	0.033	1.617(1.245–2.101)	< 0.001	1.320(1.008–1.728)	0.044
Adjuvant chemotherapy								
No								
Yes	1.294(0.970–1.726)	0.08			1.348(1.036–1.756)	0.026	0.873(0.650–1.173)	0.369
LDH(IU/L)								
Mean ± SD	1.004(1.001–1.007)	0.002	1.003(1.000–1.006)	0.067	1.003(1.001–1.006)	0.009	1.002(0.999–1.005)	0.134
dNLR								
Mean ± SD	1.138(1.021–1.268)	0.019	0.913(0.775–1.076)	0.276	1.107(0.998–1.228)	0.055		
IPI group								
Low								
High	2.020(1.495–2.731)	< 0.001	1.886(1.323–2.689)	< 0.001	1.785(1.362–2.340)	< 0.001	1.500(1.121–2.009)	0.006

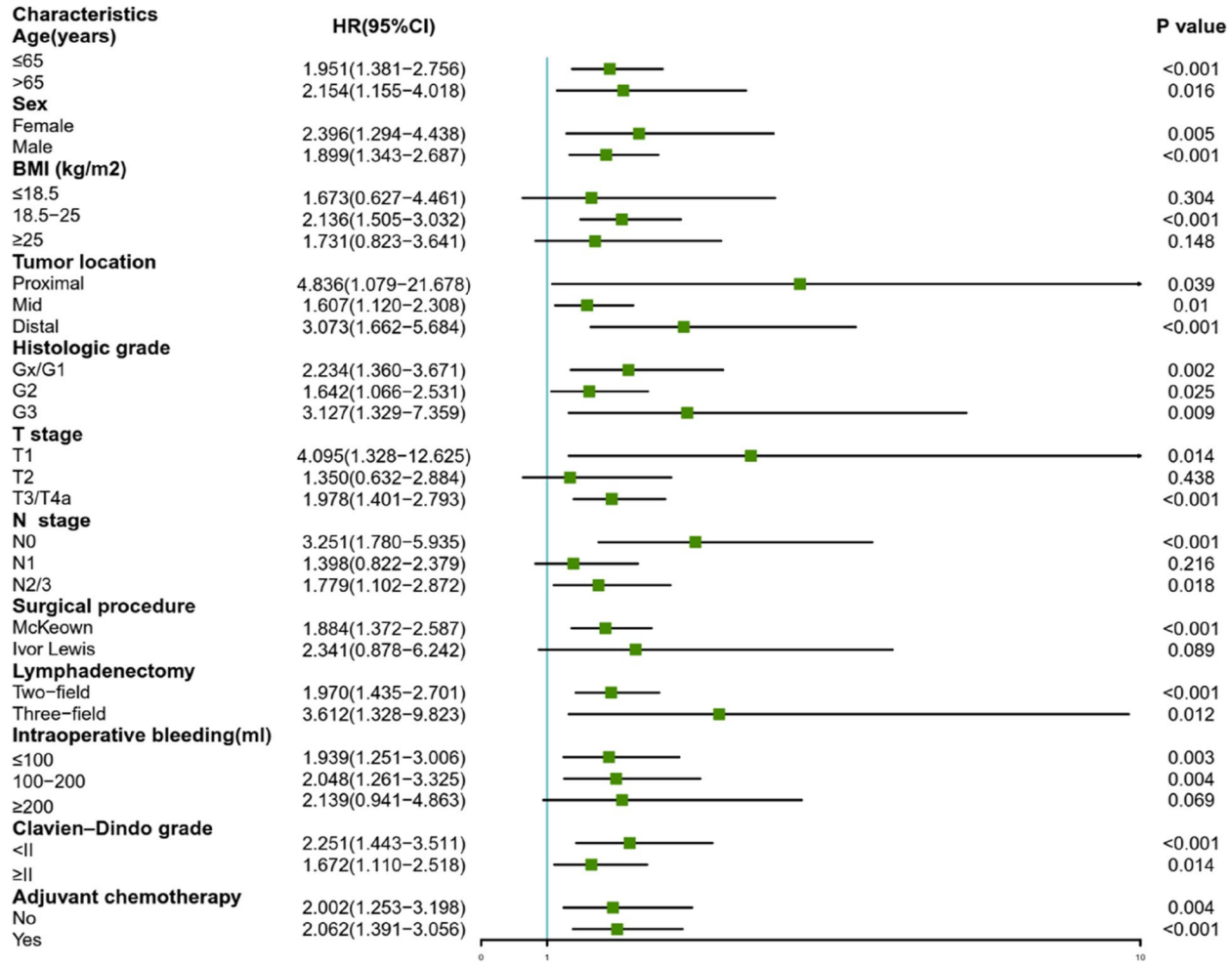

Fig.3 Forest plot for subgroup analysis to assess the association between the preoperative IPI and OS in the PSM cohort

defined patients with IPI =0 as the low IPI group and patients with score =1 or 2 as the high IPI group. Using multivariate Cox and PSM analyses, we systematically verified the good predictive value of IPI for the survival of ESCC after MIE. IPI, as a potential marker of peripheral inflammation, not only affected OS and DFS in the overall cohort but also in the matched cohort. Further ROC analysis revealed that IPI combined with dNLR or LDH had better predictive performance than either dNLR or LDH alone and that it could be used to build a relatively ideal predictive model.

Despite there being no consensus on AC after radical resection of ESCC, some evidence suggests that relapse is a major cause of treatment failure in ESCC patients, occurring in more than 50% of patients after surgery, and the median time to recurrence is 2 years [44, 45]. Therefore, it is critical to explore the utility of AC in ESCC patients as well as to identify the patient population that would benefit. In a recent PSM study, the researchers found that AC prolonged the median OS from 28.0 to 54.0 months and the median DFS from 22.0 to 33.0 months in postoperative node-positive ESCC patients [18]. Furthermore, in another study of patients with node-negative ESCC who underwent AC, the 5-year OS increased from 69.7% to 75.6% and the 5-year DFS increased from 48.2% to 64.9% when compared to surgery alone [46]. Deng et al. developed and validated the AC-based nomogram, which can improve the prognosis of patients and AC can increase 5-year OS by at least 10%, providing evidence for the benefit of AC [47]. Similar to these studies, our findings revealed that only patients with stage III ESCC who received AC had improved survival outcomes than those who received only surgery (Fig.S6).

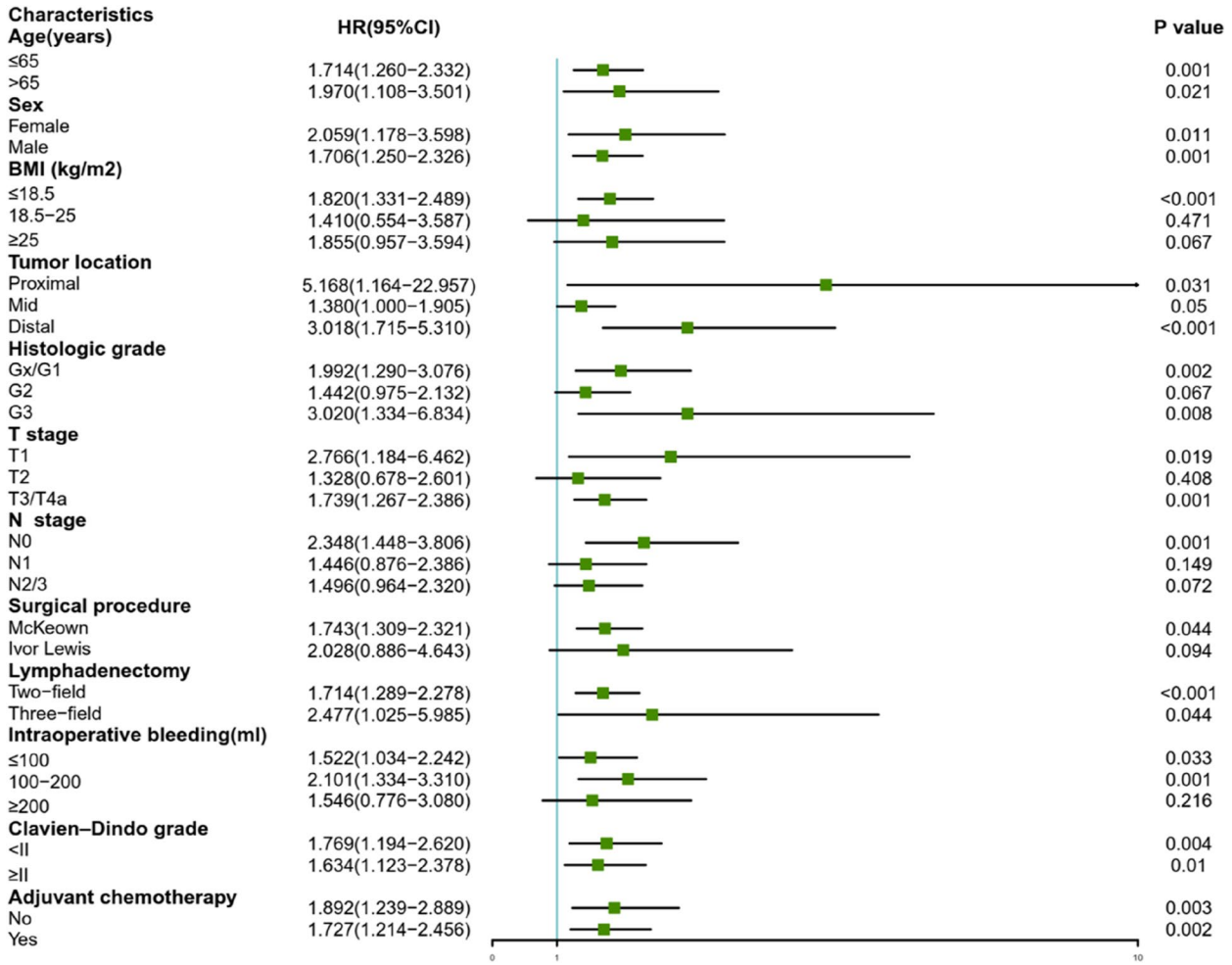

Fig. 4 Forest plot for subgroup analysis to assess the association between the preoperative IPI and DFS in the PSM cohort

The pathological TNM staging is an important tool for determining whether patients should be treated with AC. However, the majority of these decisions are based solely on the characteristics of the tumor, ignoring the impact of the tumor's microenvironment. After differentiation, neutrophils in the tumor microenvironment will develop different phenotypes and functional polarization states, allowing them to play either tumor inhibition or tumor promotion roles [48]. The inflammatory environment induces a phenomenon called"emergency granulopoiesis", in which the rapid production of immature or poorly differentiated neutrophils leads to tumor invasion [49]. IPI includes dNLR and LDH to reflect the degree of immune inflammation in the body's periphery, which can provide more information than the TNM stage. Accordingly, we found that stage III patients with high IPI received survival benefits from AC, whereas patients with low IPI did not. This could be because the immune inflammatory microenvironment in patients with low IPI is good and has formed an effective antitumor state. AC does not further improve the survival rate of patients.

Preoperative IPI demonstrates a prognostic value in patients with ESCC following MIE for the first time, and stratified analysis revealed that platinum-based chemotherapy can improve survival in stage III patients with high IPI status. However, this study has some limitations. Using PSM, we were able to eliminate baseline differences between the low-IPI and high-IPI groups; however, the single-center retrospective analysis implied selection bias. Second, although the data from our center indicate that

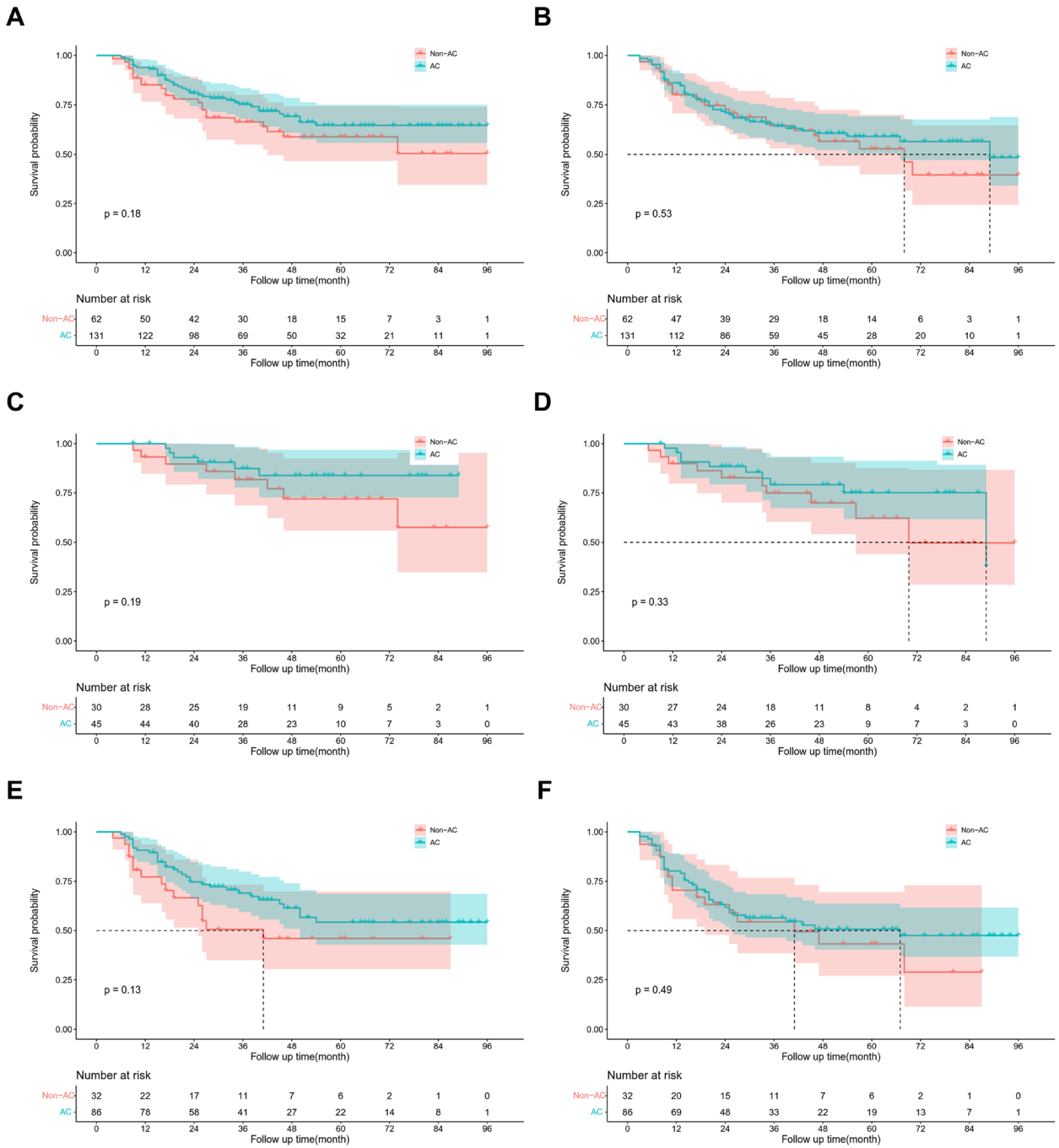

Fig. 5 Comparison of OS between the AC and Non-AC groups according to pathological stage in low IPI subpopulation of the PSM cohort. **A** Stage II-III patients with low IPI. **C** Stage II patients with low IPI. **E** Stage III patients with low IPI; Comparison of DFS between the AC and Non-AC groups according to pathological stage in low IPI subpopulation of the PSM cohort. **B** Stage II-III patients with low IPI. **D** Stage II patients with low IPI. **F** Stage III patients with low IPI

IPI is a good potential indicator for predicting the prognosis of ESCC, the results of this study must be confirmed by multicenter or prospective studies. Third, while surgery after chemical induction is the standard treatment for locally advanced ESCC, more ESCC patients in China are opting for surgery alone, so the findings of this study have limited relevance for patients receiving neoadjuvant therapy.

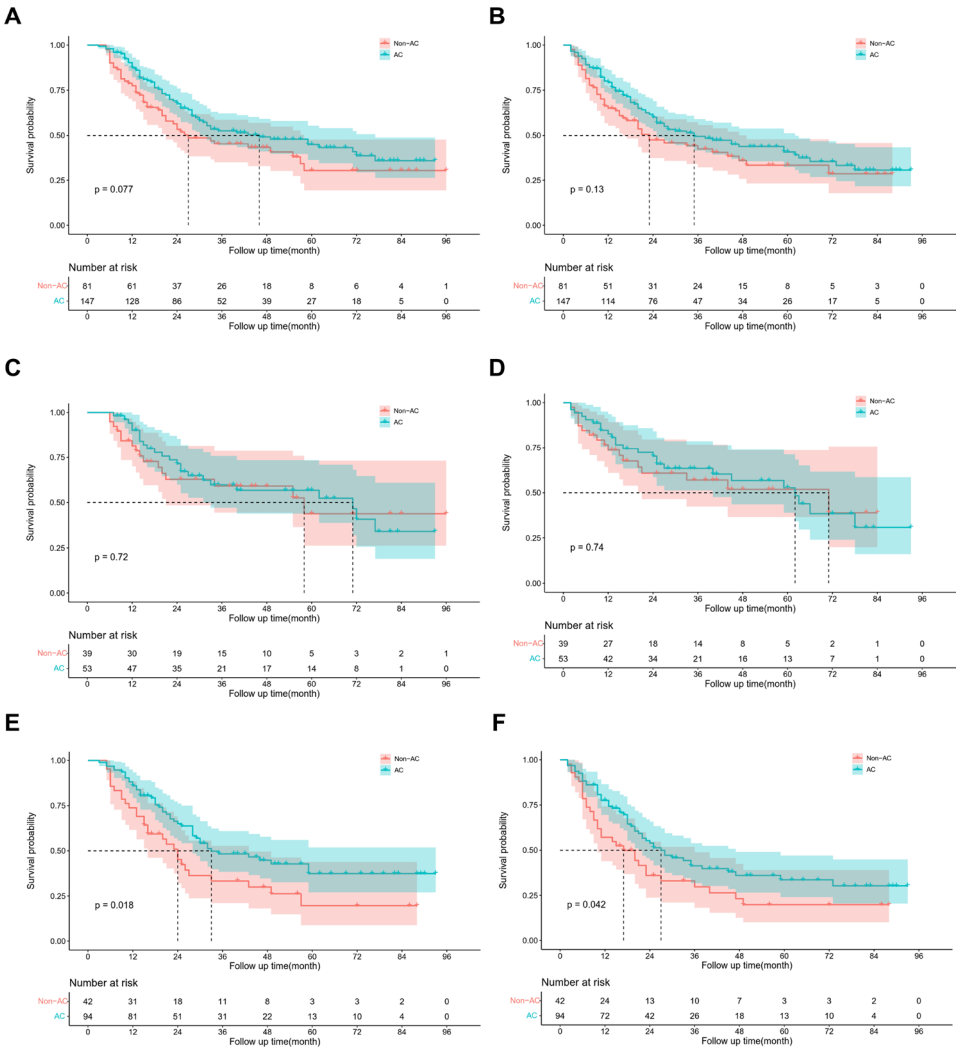

Fig. 6 Comparison of OS between the AC and Non-AC groups according to pathological stage in high IPI subpopulation of the PSM cohort. **A** Stage II-III patients with high IPI. **C** Stage II patients with high IPI. **E** Stage III patients with high IPI; Comparison of DFS between the AC and Non-AC groups according to pathological stage in high IPI subpopulation of the PSM cohort. **B** Stage II-III patients with high IPI. **D** Stage II patients with high IPI. **F** Stage III patients with high IPI

In summary, preoperative IPI was found to have a good predictive ability for OS and DFS after MIE in ESCC patients. In most clinicopathological subgroup analyses, patients in the low IPI group effectively reduced the risk of death or recurrence when compared to the high IPI group. A more in-depth analysis revealed that stage III patients in the low-IPI group did not benefit from AC, whereas patients in the high-IPI group did. In light of this, we propose routine platinum-based AC for stage III patients after MIE with high IPI.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03959-z.

Additional file 1: Fig. S1. Flow chart of patient inclusion. Fig. S2. The best cut-off values ofdNLR andLDH for OS according to X-tile in the entire cohort. Fig. S3. The best cut-off values ofdNLR andLDH for DFS according to X-tile in the entire cohort. Fig. S4. ROC curve reveals the ability of dNLR, LDH and IPI to predict OSand DFSfor 3 and 5 years in the entire cohort. Fig. S5. ROC curve reveals the ability of dNLR, LDH and IPI to predict OSand DFSfor 3 and 5 years in the PSM cohort. Fig. S6. Comparison of OS between the AC and Non-AC groups according to pathological stage in the PSM cohort.Stage II-III patients.Stage II patients.Stage III patients; Comparison of DFS between the AC and Non-AC groups according to pathological stage of the PSM cohort.Stage II-III patients.Stage II patients. Stage III patients

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Authors' contributions
Jin Huang (Co-first authors): Conceptualization, Methodology, Investigation, Formal Analysis, Writing-Original Draft; Chao Chen and Yan-Ming Shen (Co-first authors): Methodology, Investigation, Data Curation, Formal Analysis; Jin Huang: Data Curation, Writing-Original Draft; Jin Huang and Zhao-Min Sun: Visualization, Investigation; Chao Chen and Yan-Ming Shen: Resources, Supervision; Yun-Fan Luo and Jie Chen: Validation, Writing—Review & Editing. Shu-Chen Chen (Corresponding Author), Ji-Hong Lin (Corresponding Author) and Shao-Jun Xu (Corresponding Author): Conceptualization, Funding Acquisition, Resources, Supervision, Writing—Review & Editing. All authors agree to be accountable for all aspects of the work. All authors have read and approved the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. This study was reviewed and approved by the Fujian Medical University Union Hospital Institutional Ethics Review Board. All participants provided written informed consent before enrolment in the study. The consent process included a detailed explanation of the study's purpose, procedures, potential risks and benefits, and the voluntary nature of participation.

Consent for publication
Not Applicable. This manuscript does not contain any individual person's data in any form, including identifying images or personal or clinical details that could compromise anonymity. As such, no specific consent for publication was required from any individuals. All data presented in this study are aggregated and anonymized, ensuring the privacy and confidentiality of all participants involved in the research. We have adhered strictly to ethical guidelines and data protection regulations throughout the study and in the preparation of this manuscript.

Competing interests
The authors declare no competing interests.

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