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Effects of intravenous anesthesia and inhalation anesthesia on postoperative inflammatory markers in patients with esophageal cancer: a retrospective study

Jie Ren[1†], Yue Ma[2†], Ming Wei[3] and Zhiguo Li[3*]

Abstract

Background Inflammatory markers have been confirmed to be associated with the prognosis of cancer patients. In this study, we compared the impacts of intravenous anesthesia and inhalation anesthesia on the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII) after esophageal cancer surgery.

Methods We retrospectively reviewed the electronic medical records of patients who underwent esophagectomy from January 1, 2014 to December 31, 2016. Patients respectively received total intravenous anesthesia (TIVA) or inhalational anesthesia (INHA). Inverse probability of treatment weighting (IPTW) was employed to minimize differences. The Mann-Whitney U test or Kruskal Wallis test was utilized to compare the effect of the two groups on postoperative NLR, PLR and SII.

Results A total of 519 patients who had undergone esophageal cancer resection were recruited in this study, among whom 339 patients were eligible (TIVA group, $n=201$, INHA group, $n=138$). After IPTW, there was no statistically significant difference in NLR, PLR, and SII on the first postoperative day($P=0.1951$), ($P=0.5611$), ($P=0.9684$) and on the third postoperative day($P=0.5961$), ($P=0.1804$), ($P=0.9653$) between the two groups.

Conclusions In conclusion, there was no significant difference in NLR, PLR and SII between intravenous anesthesia or inhalational anesthesia. TIVA is not superior to INHA in reducing the perioperative inflammatory response of esophageal cancer.

Synopsis Inflammatory markers play an important role in the recurrence, metastasis and survival of tumor patients after surgery. In this study, we will compare the effects of different anesthesia methods on inflammatory markers.

Keywords TIVA, INHA, IPTW, Esophageal cancer, NLR, PLR, SII

[†]Jie Ren and Yue Ma contributed equally to this work.

*Correspondence:
Zhiguo Li
lizhiguo19831128@163.com

[1]Department of Anesthesiology, Guizhou Provincial People's Hospital, No.83 Zhongshan East Road, Nanming District, Guiyang, Guizhou 550002, China
[2]Department of Orthopedics, The Second Affiliated Hospital of Air Force Medical University, Xi'an, Shanxi Province 710000, China
[3]Department of Anesthesiology, Harbin Medical University Cancer Hospital, No. 150 Haping Rd., Nangang District, Harbin 150081, China

Background

Esophageal cancer (EC) is one of the most common digestive system tumors, ranking seventh in incidence worldwide and sixth in terms of mortality [1]. China is one of the regions with high incidence of esophageal cancer in the world. Esophageal squamous cell carcinoma and adenocarcinoma are the main types of the disease [2]. Despite the constant changes in the treatment of esophageal cancer, surgery remains the optimal treatment option for esophageal cancer [3]. Stress and inflammatory responses during surgical procedures contribute to the recurrence and metastasis of tumors in patients [4]. Perioperative factors (such as the method of anesthesia, anesthetic drugs, and blood transfusions) may exacerbate or mitigate this effect [5, 6]. Among them, the influence of anesthesia methods and drugs on the progression of tumor patients, as well as postoperative recurrence and metastasis has been a hot topic [7]. Compared to inhalation anesthetics such as sevoflurane, propofol may lead to a better prognosis for oncology patients because of its anti-tumor and anti-inflammatory effects [8, 9].

Inflammation plays a crucial role in cancer patients, not only facilitating immune responses but also eliciting immune suppression. [10] Some inflammatory markers can monitor the systemic inflammatory response and the dynamic balance of immunity in tumor patients, such as the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the systemic immunoinflammatory index (SII). Currently, NLR, PLR and SII are widely used to evaluate the prognosis of patients with tumors [11, 12]. Nevertheless, few studies have shown the impact of different anesthesia methods on perioperative inflammatory markers. In our study, we hypothesized that propofol-based total intravenous anesthesia has a beneficial effect on the inflammatory markers of esophageal cancer, and we compared the common inflammatory markers NLR, PLR, SII.

Methods

Inclusion and exclusion criteria for patients

Patients who underwent esophageal cancer resection at Harbin Medical University Cancer Hospital between January 1, 2014 and December 31, 2016 were collected for this study. The exclusion criteria were as follows: (1) Patients with esophageal tumors other than squamous and adenocarcinomas. (2) Emergency surgery. (3) Patients with preoperative metastases. (4) Patients with non-two anesthesia methods. (5) Patients with incomplete clinical data. We obtained the medical records of all included patients and data were extracted by researchers who were not involved in the study or data analysis.

Anesthesia technique and grouping method

According to the distinct anesthesia techniques, they were divided into total intravenous anesthesia group (TIVA) and inhalational anesthesia group (INHA). In both groups, patients underwent anesthesia induction with midazolam 0.05 ~ 0.15 mg/kg, 0.5 ug/kg fentanyl, 0.15 ~ 0.2 mg/kg cisatracurium and 1 ~ 2.5 mg/kg propofol. In the TIVA group, anesthesia was maintained with propofol and remifentanil [13]. In the INHA group, anesthesia was maintained with sevoflurane and remifentanil. The bispectral index (BIS) was maintained within the range of 40 to 60 for both anesthesia methods. During the anesthesia regimen, the mean systemic blood pressure was maintained within 20% of baseline or above 60 mmHg by using appropriate doses of vasopressors or inotropics. Patients received patient-controlled intravenous analgesia (PCIA) at dosages of 3 μg/mL of fentanyl or 0.5 μg/mL of sufentanil for 72 to 120 h after surgery.

Indicator and data

This study focused on comparing the influences of two anesthetic methods on the changes in NLR, PLR and SII on the first and third postoperative days. We gathered the following perioperative details: demographic data, concurrent disease, adjuvant therapy (radiotherapy/chemotherapy), preoperative hemoglobin (HB), American Society of Anesthesiologists (ASA) grade, duration of anesthesia, the length of the operation, surgical type, degree of differentiation, pathological classification, tumor location, cancer staging, preoperative and postoperative NLR, PLR, and SII. The criteria for cancer staging are based on the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Neutrophils, lymphocytes and platelets were collected within 3 days before surgery, the first day and the third day after surgery. NLR was defined as: NLR = neutrophil count/lymphocyte count. PLR was defined as: PLR = platelet count/lymphocyte count. SII was defined as: (platelet count × neutrophil count)/lymphocyte count.

Statistical analysis

The cases with unqualified data were excluded from the final analysis, and the cases that met the requirements of this study were statistically analyzed. Associations between categorical variables were assessed using the Fisher exact test or $\chi 2$ test. Continuous variables between patient groups were compared by T-tests or Manne Whitney U tests. Categorical data were represented by n (%), and analyzed by $\chi 2$ test, continuous data was expressed as the mean (standard deviation, SD) or median [interquartile range], and two independent samples were analyzed by T-tests. Inverse probability of treatment weighting (IPTW) was utilized to reduce the effect of confounding factors between the two groups

[14]. The weighted model included the following variables: sex, age, BMI, smoke, drink, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, ASA, adjuvant treatment, duration of anesthesia, duration of anesthesia, the length of the operation, blood transfusion, surgical type, pathological classification, degree of differentiation, tumor location, TNM, preoperative HB, preoperative NLR, preoperative PLR, preoperative SII. The balance of covariates between the TIVA and INHA groups was assessed by the standardized mean difference (SMD). An SMD < 0.1 indicated a good balance in the covariates between the two groups. All the analyses were performed by the R software (version 4.1.2). We utilized the package "survey" for inverse probability of treatment weighting. The package "ggprism", "reshape2", "tableone" were employed for graphing and p-value < 0.05 was regarded statistically significant.

Results

The clinical data of 519 patients with esophageal cancer who underwent radical resection were retrospectively examined. After the application of the inclusion criteria were applied, 201 patients assigned to the TIVA group and 138 patients to the INHA group. After IPTW, the sum of weights was 337 in the TIVA group, and 341.1 in the INHA group (Fig. 1). All standardized mean differences (SMD)for the study variables were less than 0.1 (Table 1) (Fig. 2).

In this study, NLR, PLR, and SII were collected at 1 and 3 days after surgery for comparison between the two groups. The median NLR in the TIVA and INHA groups on the first postoperative day was 13.32(interquartile range,10.78 to 15.07) vs. 13.12(interquartile range,10.5 to 14.01), there was no statistically significant difference between the two groups ($P=0.2022$). The median NLR at TIVA and INHA on the third postoperative day was 9.89(interquartile range,6.52 to 13.60) vs. 9.35(interquartile range,6.59 to 12.94), there was no statistically significant difference between the two groups ($P=0.7423$). After IPTW, there remained no significant difference in NLR between the two groups on the first ($P=0.1951$) and third postoperative days ($P=0.5961$) (Fig. 3A).

The median PLR in the TIVA and INHA groups on the first postoperative day was 302.7(interquartile range,199.5 to 398.1) vs. 291.07(interquartile range,219.38 to 387.8), there was no statistically significant difference between the two groups ($P=0.896$). The median PLR in the TIVA and INHA groups on the third postoperative day was 9.89(interquartile range,6.52 to 13.60) vs. 9.35(interquartile range,6.59 to 12.94), there was no statistically significant difference between the two groups ($P=0.4879$). After IPTW, there still remained no significant difference in PLR between the two groups on the first ($P=0.5611$) and third postoperative days ($P=0.1804$) (Fig. 3B).

The median SII in the TIVA and INHA groups on the first postoperative day was 2822.1 (interquartile range, 1993.9 to 3897.1) vs. 2747.8 (interquartile range, 1885.0 to 3900.9), there was no statistically significant difference between the two groups ($P=0.5272$). The median SII in the TIVA and INHA groups on the third postoperative day was 2626.0 (interquartile range, 1843.3 to 3860.7) vs. 2593.7 (interquartile range, 1825.0 to 3700.2), there was no statistically significant difference between the

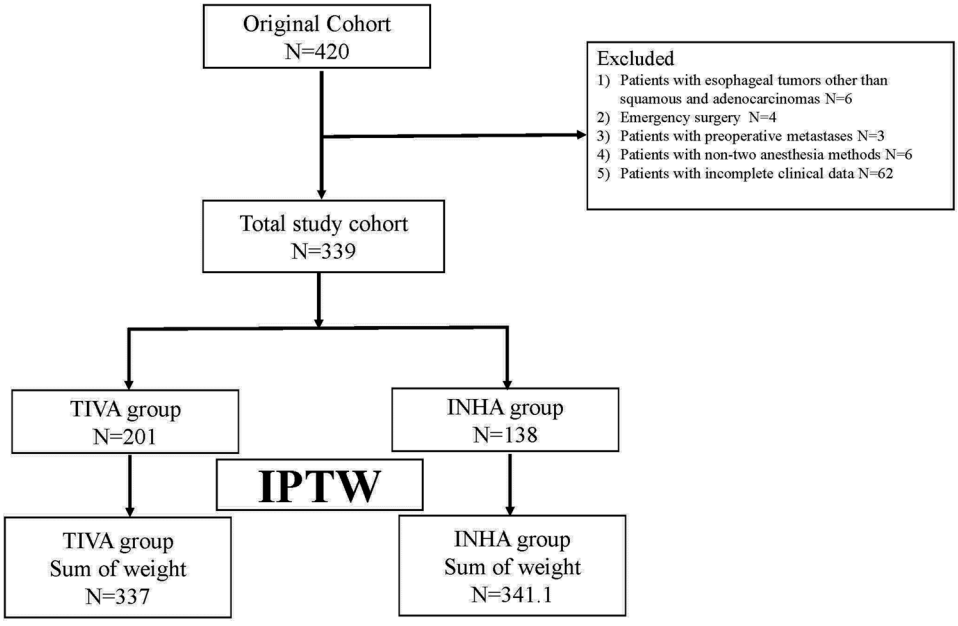

Fig. 1 Patient identification and exclusion. Abbreviations: IPTW, Inverse probability of treatment weighting

Table 1 Patient characteristics for before IPTW adjustment and after IPTW adjustment

Variable	Before IPTW adjustment			After IPTW adjustment			
	TIVA	INHA	*P*	TIVA	INHA	*P*	SMD
				Sum of weight	Sum of weight		
	n = 201	*n* = 138		*n* = 337	*n* = 341.1		
Sex (%)							
Female	5 (2.5)	4 (2.9)	1	7.0 (2.1)	11.8 (3.4)	0.451	0.083
Male	196 (97.5)	134 (97.1)		330.0 (97.9)	329.3 (96.6)		
Age	59	58	0.525	58.93	58		
(median [IQR], year)	[53.00, 63.00]	[53.00, 62.00]		[53.00, 63.00]	[53.00, 63.00]	0.992	0.02
BMI	22.09	22.49	0.472	22.15	22.1		
(median [IQR], kg/m2)	[20.08, 24.82]	[20.29, 24.24]		[20.08, 25.09]	[20.28, 24.18]	0.641	0.012
Smoke (%)							
No	79 (39.3)	48 (34.8)	0.465	127.0 (37.7)	126.6 (37.1)	0.92	0.012
Yes	122 (60.7)	90 (65.2)		210.0 (62.3)	214.5 (62.9)		
Drink (%)							
No	68 (33.8)	42 (30.4)	0.591	109.2 (32.4)	112.1 (32.9)	0.934	0.01
Yes	133 (66.2)	96 (69.6)		227.8 (67.6)	229.0 (67.1)		
Hypertension (%)							
No	173 (86.1)	112 (81.2)	0.288	283.5 (84.1)	287.6 (84.3)	0.959	0.006
Yes	28 (13.9)	26 (18.8)		53.5 (15.9)	53.5 (15.7)		
Diabetes (%)							
No	197 (98.0)	131 (94.9)	0.207	325.0 (96.4)	329.5 (96.6)	0.935	0.01
Yes	4 (2.0)	7 (5.1)		12.0 (3.6)	11.6 (3.4)		
Cardiovascular disease (%)							
No	195 (97.0)	135 (97.8)	0.91	327.8 (97.3)	331.0 (97.0)	0.915	0.013
Yes	6 (3.0)	3 (2.2)		9.2 (2.7)	10.1 (3.0)		
Cerebrovascular disease (%)							
No	191 (95.0)	127 (92.0)	0.371	316.6 (94.0)	320.2 (93.9)	0.979	0.003
Yes	10 (5.0)	11 (8.0)		20.4 (6.0)	20.8 (6.1)		
ASA (%)							
I	37 (18.4)	19 (13.8)	0.308	56.6 (16.8)	55.6 (16.3)	0.99	0.016
II	146 (72.6)	101 (73.2)		245.9 (73.0)	249.5 (73.1)		
III	18 (9.0)	18 (13.0)		34.5 (10.2)	36.0 (10.6)		
Adjuvant treatment (%)							
No	113 (56.2)	72 (52.2)	0.533	184.3 (54.7)	187.4 (55.0)	0.963	0.005
Yes	88 (43.8)	66 (47.8)		152.7 (45.3)	153.6 (45.0)		
Duration of anesthesia	6.08	6.29		6.17	6.17		
(median [IQR], h)	[5.00, 7.00]	[5.17, 7.40]	0.265	[5.00, 7.09]	[5.06, 7.25]	0.876	0.006
Duration of surgery	5.17	5.25		5.17	5.13		
(median [IQR], h)	[4.00, 6.08]	[3.94, 6.40]	0.214	[4.08, 6.21]	[3.83, 6.13]	0.816	0.007
Blood transfusion (%)							
No	191 (95.0)	136 (98.6)	0.154	324.9 (96.4)	329.5 (96.6)	0.943	0.01
Yes	10 (5.0)	2 (1.4)		12.1 (3.6)	11.6 (3.4)		
Surgical type (%)							
Ivor Lewis	79 (39.3)	53 (38.4)	0.823	129.3 (38.4)	127.2 (37.3)	0.994	0.03
MMcKeown	49 (24.4)	35 (25.4)		83.5 (24.8)	85.3 (25.0)		
Sweet	72 (35.8)	48 (34.8)		122.1 (36.2)	125.8 (36.9)		
Thoracoa	1 (0.5)	2 (1.4)		2.0 (0.6)	2.7 (0.8)		
Pathological classification (%)							
adenocarcinoma	5 (2.5)	3 (2.2)	1	7.1 (2.1)	6.3 (1.9)	0.859	0.019
Squamous carcinoma	196 (97.5)	135 (97.8)		329.8 (97.9)	334.7 (98.1)		
Degree of differentiation (%)							
G1	41 (20.4)	25 (18.1)	0.651	64.4 (19.1)	61.1 (17.9)	0.963	0.031
G2	93 (46.3)	62 (44.9)		156.4 (46.4)	161.9 (47.5)		

Table 1 (continued)

Variable	Before IPTW adjustment			After IPTW adjustment			
	TIVA	INHA	*P*	TIVA	INHA	*P*	SMD
				Sum of weight	Sum of weight		
	n = 201	*n* = 138		*n* = 337	*n* = 341.1		
G3	67 (33.3)	51 (37.0)		116.2 (34.5)	118.0 (34.6)		
Tumour location (%)							
Bottom	90 (44.8)	64 (46.4)	0.756	151.2 (44.9)	147.4 (43.2)	0.957	0.034
Middle	97 (48.3)	62 (44.9)		158.5 (47.0)	166.0 (48.7)		
Top	14 (7.0)	12 (8.7)		27.3 (8.1)	27.6 (8.1)		
TNM (%)							
I	44 (21.9)	22 (15.9)	0.308	65.3 (19.4)	64.7 (19.0)	0.99	0.016
II	69 (34.3)	46 (33.3)		114.2 (33.9)	118.2 (34.6)		
III	88 (43.8)	70 (50.7)		157.4 (46.7)	158.1 (46.4)		
Pre.HB	145	145.45	0.439	146.03	145.04		
(median [IQR])	[135.20, 153.70]	[137.12, 154.95]		[136.24, 154.00]	[137.00, 154.65]	0.896	0.004
Pre.PLR	121.83	121.92	0.82	121.93	117.11		
(median [IQR])	[99.48, 148.84]	[90.51, 162.02]		[99.54, 148.82]	[86.59, 152.20]	0.312	0.02
Pre.NLR	1.97	1.98	0.528	1.96	1.97		
(median [IQR])	[1.55, 2.81]	[1.56, 2.62]		[1.53, 2.76]	[1.56, 2.60]	0.544	0.032
Pre.SII	469.62	455.86	0.467	463.51	439.45		
(median [IQR])	[346.50, 704.19]	[324.30, 635.68]		[347.59, 700.55]	[313.07, 615.04]	0.179	0.026

Abbreviations: IQR, inter-quartile range; Cancer stages: stage I: T1, N0, M0/T2, N0, M0/T1, N1, M0; stage II: T3, N0, M0/T4a, N1, M0/T3, N1, M0/T2, N2, M0/T1, N3, M0; stage III: T2, N3, M0/T3, N2, M0/T3, N3, M0/T4a, N2, M0/T4a, N3, M0/any T4b, any N, M0; stage IV: any T, any N, M1.ASA, American Society of Anesthesiologists; BMI, body mass index; INHA, inhalational anesthesia; TIVA, total intravenous anesthesia, IPTW, inverse probability of treatment weighting; SMD, Standardized Mean Difference; Pre, preoperative; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammatory index

Because the weighted values were presented, the number of patients were not an integer

two groups (P=0.698). After IPTW, there was no significant difference in SII between the two groups on the first (P=0.9684) and third postoperative days (P=0.9653) (Fig. 3C).

Discussion

This study showed that there was no difference in the effects of propofol-based total intravenous anesthesia and sevoflurane-based inhalation anesthesia on NLR, PLR, and SII at 1 and 3 days after surgery in EC surgery. The choice of anesthesia method may have no impact on the inflammatory markers in EC patients.

It is well known that systemic inflammation and immunity play an important role in tumor progression [10]. NLR, PLR, and SII are inflammatory markers based on common peripheral blood cells, and they reflect the relative changes between systemic inflammation and immunity. The higher the perioperative NLR, the worse the prognosis of cancer patients [15, 16]. This may be attributed to a higher tendency for intratumoral neutrophils in patients with high NLR [17]. Intratumoral neutrophils promote tumor cell growth and metastasis through paracrine [18]. PLR has also been demonstrated to be a potent marker of systemic inflammation, and high PLR is associated with distant metastasis in patients with tumors [19, 20]. The main cause for this is that platelets protect tumor cells within the circulatory system from immune elimination and promote tumor cell metastasis [21]. However, these two inflammatory markers integrate only two cell types. SII is a new inflammatory marker proposed by Hu et al., which includes neutrophils, platelets and lymphocytes [22]. The prognosis of patients with SII tumors is predicted by the function of the three cell types and their close relationship with circulating tumor cells (CTCs), which play a significant role in the initiation of postoperative recurrence and metastasis [23]. Compared to NLR, PLR, SII can reflect the link between inflammation, immunity and tumor more effectively and comprehensively [11, 12, 24].

In our study, we discovered that propofol-based total intravenous anesthesia, when compared with sevoflurane-based inhalation anesthesia, failed to reduce NLR in EC patients on the first and third postoperative days. This is similar to the results of a recent prospective study on colorectal cancer. In this study, propofol anesthesia compared to sevoflurane did not reduce postoperative NLR levels in colorectal cancer patients at 1 and 24 h [25]. It is possible that clinical doses of anesthetic drugs have a restricted effect on reducing immunosuppression and inflammation. Another retrospective study on postoperative NLR in colorectal cancer found that NLR levels were decreased in the TIVA group at 1, 2, and 5 days after surgery [26]. The results of the above study are contrary to ours, which may be attributed to differences in tumor

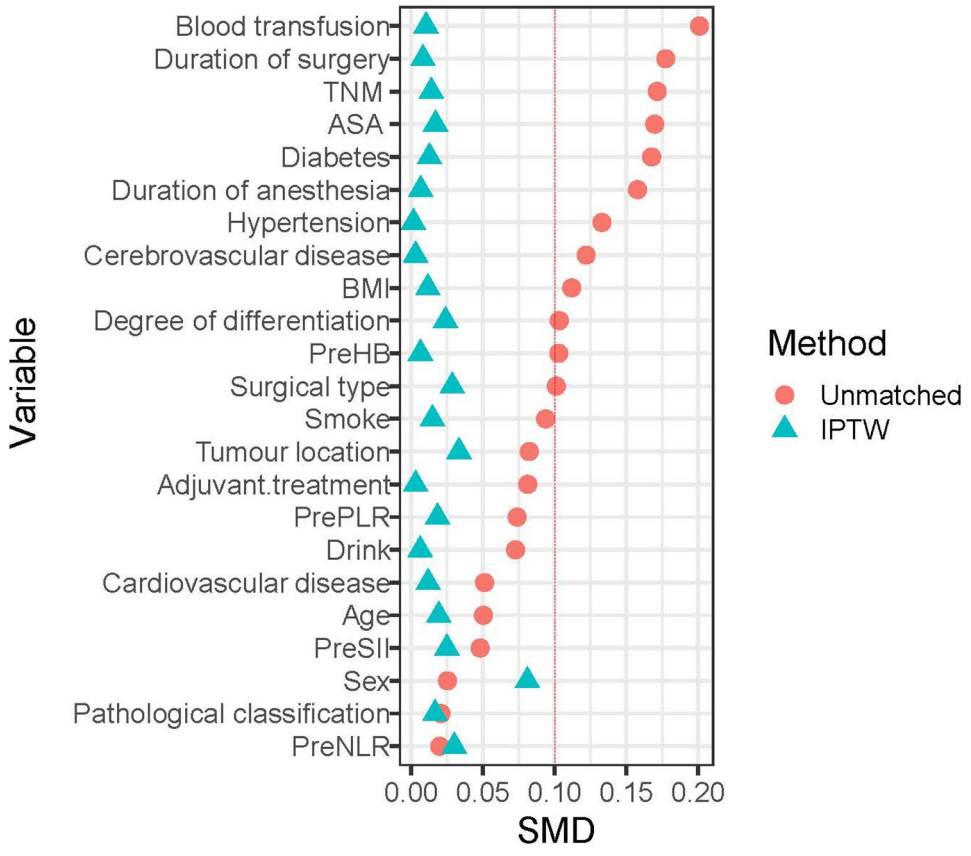

Fig. 2 The distribution of standardized mean difference for variables included before and after matching. **Abbreviations**: Cancer stages: stage I: T1, N0, M0/T2, N0, M0/T1, N1, M0; stage II: T3, N0, M0/T4a, N1, M0/T3, N1, M0/T2, N2, M0/T1, N3, M0; stage III: T2, N3, M0/T3, N2, M0/T3, N3, M0/T4a, N2, M0/T4a, N3, M0/any T4b, any N, M0; stage IV: any T, any N, M1.ASA, American Society of Anesthesiologists; BMI, body mass index; Pre, preoperative; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammatory index

and type of surgery. In addition, retrospective studies often use propensity score matching to reduce confounding, which may result in distinct outcomes with some significant missing data. In our research, we utilized the method of IPTW [14] to minimize confounding factors without reducing the amount of data, and the statistical results were more convincing. Similarly, we investigated PLR and SII in EC patients on the first and third postoperative days. The outcomes demonstrated that clinical concentrations of propofol anesthesia did not provide an advantage over sevoflurane-based anesthesia in short-term postoperative PLR and SII.

Propofol is a commonly utilized anesthetic, and its immune and inflammatory effects on cancer patients have been a heated topic [27, 28]. In the domain of immunity, one study revealed that propofol-based total intravenous anesthesia significantly increased postoperative NKCC (Natural killer cell cytotoxicity) in breast cancer patients [29]. In another study comparing the immune effects of propofol and sevoflurane in cervical cancer, the postoperative sevoflurane group had significantly lower CD3+cells, CD4+cells, NK cells, and CD4+/CD8+ratios than the TIVA group [30]. Conversely, some studies have indicated that the function of immune cells including natural killer cells and T lymphocytes is not influenced by sevoflurane and propofol anesthesia [31, 32]. Gu et al. also claimed in the review that propofol may be more beneficial than sevoflurane and isoflurane in terms of tumor postoperative immune regulation, but there is still some disagreement and more randomized clinical trials are needed [33]. In terms of inflammation, in vitro experiments disclosed that propofol, compared with sevoflurane, reduced inflammatory responses through the NF-κB signaling pathway and induced apoptosis in human neuroglioma cells [34]. In clinical practice, O'Bryan et al. noted in a meta-analysis that the choice of anesthesia method has little effect on the inflammatory response during the perioperative period [35]. The available data demonstrating the effect of anesthesia on inflammation in vitro and in vivo studies are still controversial. The above might explain the fact that postoperative inflammatory markers in EC patients did not show significant differences between the two anesthesia methods.

There are certain inevitable limitations to our study. Firstly, the study only included a few inflammatory

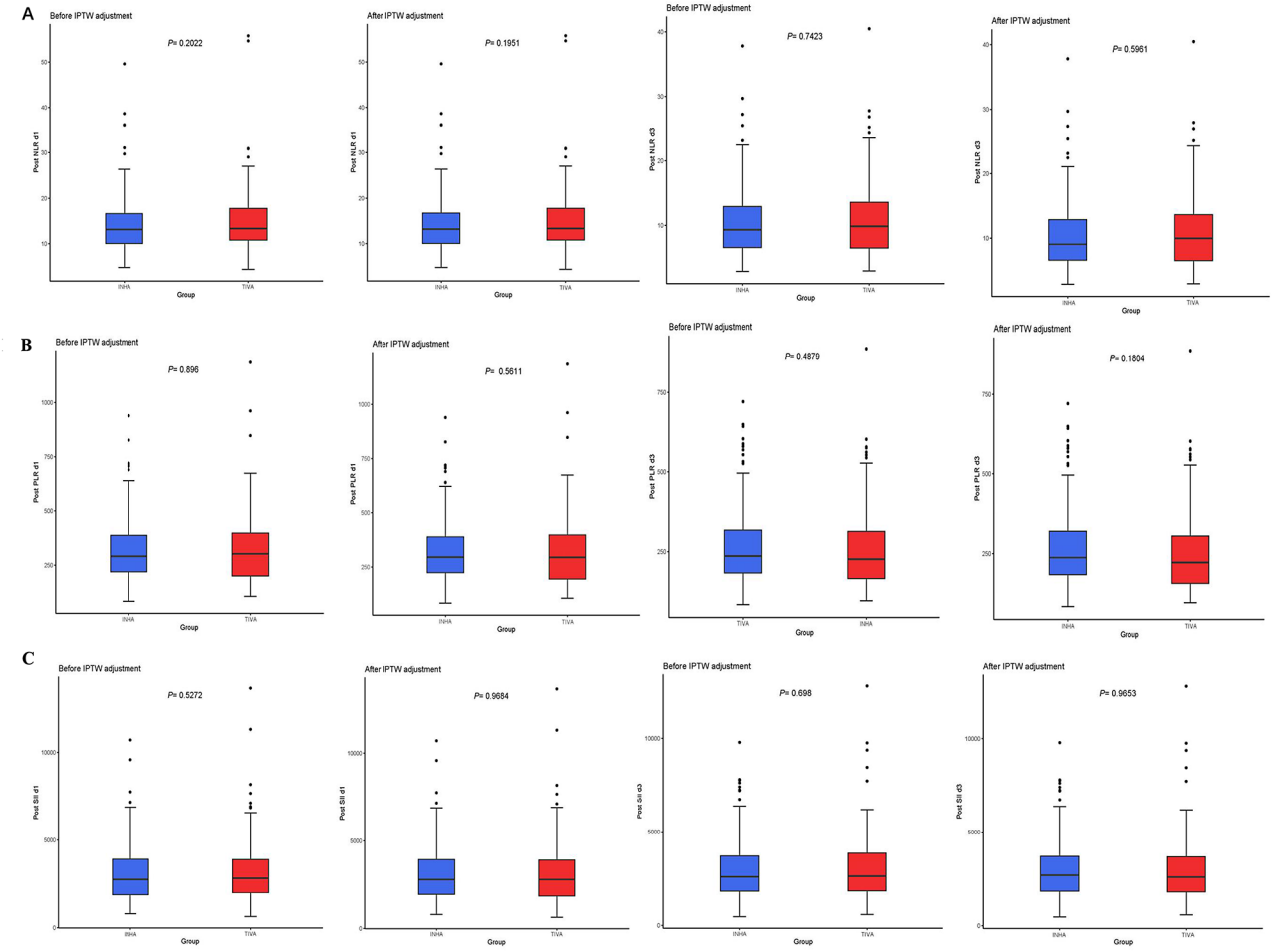

Fig. 3 (**A**) Postoperative NLR at 1 and 3 days before and after IPTW adjustment. 3(**B**). Postoperative PLR at 1 and 3 days before and after IPTW adjustment. 3 (**C**). Postoperative SII at 1 and 3 days before and after IPTW adjustment. Abbreviations: NLR, neutrophil to lymphocyte ratio. PLR, platelet to lymphocyte ratio. SII, systemic immune-inflammatory index

markers (NLR, PLR, SII), which may not comprehensively reflect the entire spectrum of perioperative inflammatory and immune responses. Secondly, the study acknowledges missing data regarding the amount of opioid used, which could significantly influence postoperative inflammatory responses and affect the study outcomes. Thirdly, since the data were collected from a single hospital, the study may lack generalizability. The findings may not apply to different populations or hospitals with varying practices.

In conclusion, TIVA and INHA had no impact on NLR, PLR and SII in patients with EC. This suggests that numerous perioperative factors may influence the inflammatory response in patients with esophageal cancer, and our study demonstrates that the type of anesthesia has a negligible effect on it.

Abbreviations

EC	Esophageal cancer
IPTW	Inverse probability of treatment weighting
TIVA	Total intravenous anesthesia
INHA	Inhalational anesthesia
NLR	Neutrophil to lymphocyte ratio
PLR	Platelet to lymphocyte ratio
SII	Systemic immune-inflammatory index
ASA	American Society of Anesthesiologists
AJCC	American Joint Committee on Cancer
CTC	Circulating tumor cell

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Author contributions

Z.L. had contributions to study conception, design. J.R. and Y.M. drafting the article and acquisition of data.M.W. had contributions to interpretation of data. Z.L. had responsibility for the revision of important intellectual content and final approval of the version to be published.All authors reviewed the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published. article.

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the ethical principles of the Declaration of Helsinki. The study procedures were approved by the Ethics Committee of The Harbin Medical University Cancer Hospital. This is a retrospective study and individual informed consent to participate for this retrospective analysis with routine clinical data was waived by the Ethics Committee of The Harbin Medical University Cancer Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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