



High level of neutrophil to lymphocyte ratio increases the risk of deep venous thrombosis in intensive care unit patients after oral cancer surgery: a retrospective study

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Background: The incidence of deep venous thrombosis (DVT) is higher in surgical patients, but there have been few studies on the risk factors of DVT in intensive care unit (ICU) patients after oral cancer surgery, particularly in relation to the inflammatory and nutritional scores, and intervene with these risk factors early may decrease the occurrence of DVT.

Methods: We performed a retrospective study of adult patients who were admitted to ICU after undergoing radical resection of oral cancer and performed ultrasound detection for DVT within 1 week after surgery from April 2019 to July 2021. DVT was diagnosed by venous ultrasonography of the lower extremities. Preoperative inflammatory and nutritional scores, including neutrophil to lymphocyte ratio (NLR), plate to lymphocyte ratio (PLR), prognostic nutritional index (PNI) were retrospectively calculated according to test results before surgery. Clinical characteristics, including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Caprini Risk Score (CRS), Charlson comorbidity index, anticoagulation therapy, and mechanical ventilation time (MVT) after admitted to ICU were obtained. The risk factors affecting DVT occurrence were analyzed by logistic regression, and the receiver operating characteristic (ROC) curve was used to analyze the value of the relevant indicators in evaluating DVT.

Results: Among the 128 patients, 43 patients (33.6%) developed DVT. Compared with the non-DVT group, the preoperative glucose (GLU), postoperative D-dimer ($P < 0.05$), and postoperative NLR ($P < 0.001$) were higher in the DVT group than in the non-DVT group. In multivariate logistic analysis, NLR ($P = 0.001$), postoperative D-dimer $> 5.57 \mu\text{g/mL}$ ($P = 0.002$), GLU $> 5.15 \text{ mmol/L}$ ($P = 0.025$) was associated with DVT, and the areas under the curve (AUCs) of NLR in predicting DVT was 0.729. We also found that the DVT group had longer MVT and length of stay (LOS) than the non-DVT group, and correlation analysis indicated that NLR level was positively related with MVT ($r = 0.36$; $P < 0.0001$) and LOS ($r = 0.452$; $P < 0.0001$).

Conclusions: A high level of NLR, indicative of a poor immunity and nutrition status, increases the risk of DVT in patients after oral cancer surgery, and improvement of immunity and nutrition status may help decrease the occurrence of postoperative DVT.

Keywords: Neutrophil to lymphocyte ratio; deep venous thrombosis (DVT); intensive care unit (ICU); oral cancer

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Introduction

Thrombosis is a common complication of tumor patients after surgery. Deep venous thrombosis (DVT) not only affects postoperative recovery, but may even cause life-threatening pulmonary embolism in severe cases. Therefore, evaluation and prevention of DVT have great clinical significance.

The incidence rate of head and neck tumors has been reported at about 0.16–3.125% (1), and oral cancer is the most common type of head and neck tumor (2). Post-surgical oral cancer patients have a lower risk of DVT when early mobilization is implemented. However, to the best of our knowledge, there has been no report about the incidence and risk factors of DVT in patients with oral cancer who are admitted to the intensive care unit (ICU) after surgery.

DVT is an intravascular blood clotting disorder, typically occurs in association with critical illnesses such as sepsis, diabetes, hypertension, cancer, autoimmune disease and ICU patients (3). In addition to classical deep vein thrombosis triggers, Virchow's triad (blood flow disturbance, hypercoagulability, and vessel wall changes), inflammation is intimately related with coagulation activation and then promotes DVT (4), especially the cascade of inflammatory cytokines and chemokines, which are initiated by inflammation dysfunctional lymphocytes, provoked neutrophil, macrophage aggregation and platelet activation (5,6). It is recently shown that neutrophils can produce neutrophil extracellular traps (NETs), which are highly prothrombotic (7). There are many mechanisms that link platelets with DVT, including that platelets contain polyphosphates, which act as proinflammatory mediators and contact system activators (8). Studies also indicate that albumin can inactivate thromboxane A₂ and inhibits platelet aggregation (9), and albumin also binds to antithrombin and enhances neutralization of coagulation factor Xa (10), so hypoalbuminemia may reflect a hypercoagulable tendency and cause the development of VTE (11).

The patients with oral cancer are often malnourished and have diminished immunity. The inflammatory and nutritional scores, including prognostic nutritional index (PNI), neutrophil to lymphocyte ratio (NLR), and plate to lymphocyte ratio (PLR) are biomarkers for systemic inflammation in various studies and have also been found to be related to venous thromboembolism (VTE). The PNI is a simple indicator of patients' nutritional status

and immune function, which was initially developed as an indicator of preoperative nutritional status of patients with a gastric or colorectal malignancy. In recent years, PNI had also been used to assess the preoperative immune function and nutritional status of patients with oral cancer (12), and moreover, PNI can predict the development of DVT after pancreatic surgery (13). Other inflammatory and nutritional indicators, such as the NLR (14) and PLR (15) have been reported to be associated with postoperative VTE after total knee replacement and oral cancer surgery, respectively. However, it is unclear whether the inflammatory and nutritional scores are associated with the occurrence of DVT in ICU patients after oral cancer surgery. In the present study, we explored the risk factors of DVT in ICU patients after oral cancer surgery, particularly in relation to the inflammatory and nutritional scores, and evaluated their independent relationship with DVT after adjustment for demographics and surgery-related characteristics. We present the following article in accordance with the STROBE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-2453/rc>).

Methods

Patients

We performed a retrospective study of adult patients who were admitted to ICU after undergoing radical resection of oral cancer and performed ultrasound detection for DVT within 1 week after surgery from April 2019 to July 2021 at the Department of Intensive Care Unit, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China. In this study, 135 patients were admitted to the ICU with oral cancer. Among them, 5 patients were excluded because they did not undergo radical resection, and a further 2 cases were excluded because they did not undergo ultrasound examination (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional Ethics Committee of Sun Yat-sen Memorial Hospital (No. SYSEC-KY-KS-2021-188). Individual consent for this retrospective analysis was waived.

Data collection

Epidemiologic data were retrospectively gathered from electronic medical records, including the patients' age,

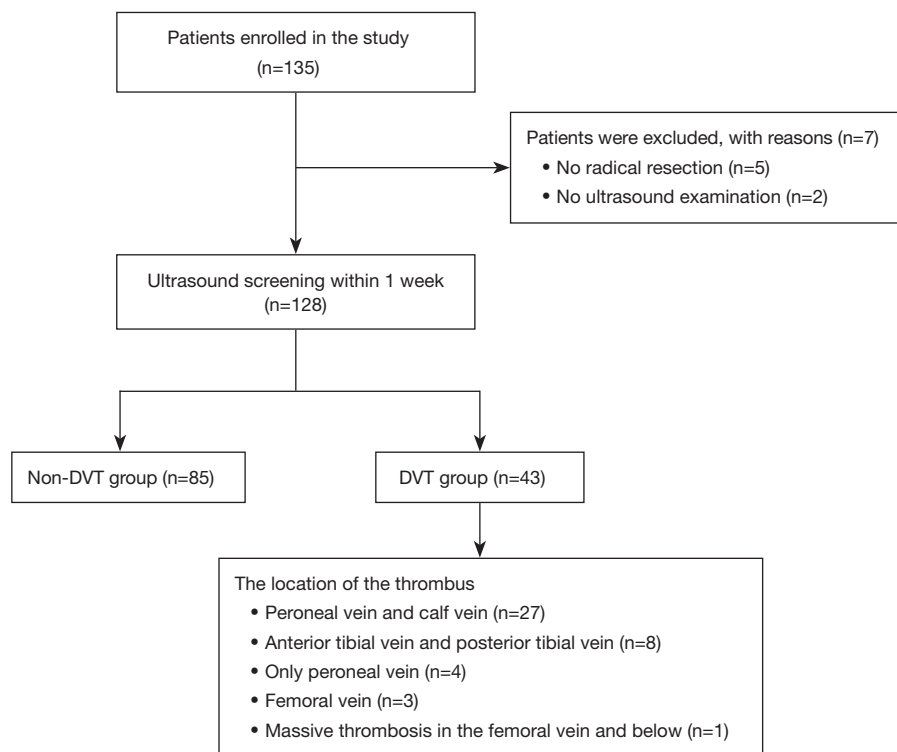


Figure 1 The workflow of patients in our study. DVT, deep venous thrombosis.

gender, body mass index (BMI), history of radiotherapy and chemotherapy, surgical and perioperative variables, and pre- and post-operative laboratory data. The disease severity evaluated by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Charlson comorbidity index, and DVT risk score evaluated by Caprini Risk Score (CRS) were retrospectively obtained for each patient. Preoperative inflammatory and nutritional scores, such as PLR, NLR, and PNI, were also retrospectively calculated. Venous ultrasonography of the lower extremities was performed by an experienced sonographer to determine the incidence and location of DVT within 1 week after admission to the ICU.

Postoperative prophylaxis of DVT

We adhered to the current standard practice for perioperative DVT prevention. The practice consisted of early postoperative mobilization of the lower extremities in bed, graduated compression stockings, and a foot pump for mechanical prophylaxis. All patients received mechanical prophylaxis, but those who underwent fibula flap reconstruction received the above treatment only on

the side contralateral to the donor. Pharmacologic VTE prophylaxis was prescribed in our unit.

Statistical analysis

The clinical records of the included cases were collected and retrospectively reviewed. The primary outcome variable was DVT. Quantitative variables with a normal distribution were expressed as mean \pm SD and with abnormal distribution were expressed as median with interquartile range. Comparison was made between patients with or without DVT using the χ^2 test for discrete variables and Student's *t*-test or Mann-Whitney U test for continuous variables. The independent association of NLR with DVT after adjustment for other variables with a stepwise method was investigated by multiple logistic regression analyses. A receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic sensitivity, specificity, and optimal cutoff value of each index. Logistic analyses were conducted to evaluate the relative influences of these variables. All statistical analyses were performed using the software SPSS 26.0 for Macintosh (IBM Corp., Armonk, NY, USA). A two-sided P value less than 0.05 was

considered statistically significant.

Results

There were 135 patients admitted to the ICU after having undergone oral cancer surgery, and 128 cases were ultimately included in the study (Figure 1). The clinical characteristics of the 128 cases are listed in Table 1. Of the 128 cases, 43 patients (33.6%) developed DVT. There was no significant difference in age, BMI, gender, APACHE II score, medical history [including chemoradiotherapy history, diabetes history, hypertension history, coronary heart disease (CHD) history], surgical variables (including operative time, blood loss, flap type), and anticoagulation therapy between the patients with DVT or without DVT ($P>0.05$). Compared with the non-DVT group, the preoperative glucose [GLU; 5.65 (4.90–7.23) vs. 4.90 (4.58–5.90) mmol/L, $P=0.017$] and postoperative D-dimer [5.81 (2.73–10.61) vs. 3.64 (1.92–6.16) $\mu\text{g/mL}$, $P=0.009$] were higher in the DVT group, while the preoperative levels of activated partial thromboplastin time (APTT), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), creatine, D-dimer, albumin, and postoperative level of albumin were not different between the DVT patients and the non-DVT patients. The CRS was surprisingly not different between the two groups, but was at a high level in both groups (Table 1). Among the preoperative nutritional and inflammatory scores, the preoperative NLR was obviously higher in the DVT group than the non-DVT group [4.60 (2.50–9.52) vs. 2.54 (1.66–4.29), $P<0.001$], while the PLR and PNI level were similar between the two groups (Table 2). We also retrospectively obtained the mechanical ventilation time (MVT) in the ICU and the length of stay (LOS) in hospital to evaluate the prognosis for each patient, and found that the DVT group had longer MVT and LOS than the non-DVT group (Table 1).

According to the ROC curve analysis of MVT, preoperative D-dimer, postoperative D-dimer, and GLU, the cut-off values were calculated as shown in Table 3. The results of multivariate logistic regression analysis showed that NLR level [odds ratio (OR) =1.342; $P=0.001$], preoperative GLU >5.15 mmol/L (OR =3.061; $P=0.025$), and postoperative D-dimer >5.57 $\mu\text{g/mL}$ (OR =4.766; $P=0.002$) were independently associated with DVT (Table 4). The area under the ROC curve (AUROC) of the NLR level in predicting DVT was 0.729 (Figure 2).

The DVT group had poorer prognosis than the non-

DVT group because the DVT group had longer MVT and LOS than the non-DVT group, as shown in Table 1. We then assessed the correlation of NLR level with the prognostic indicators using correlation analysis, and the results indicated that NLR level was positively related with MVT ($r=0.36$; $P<0.0001$) and LOS ($r=0.452$; $P<0.0001$) (Figure 3).

Discussion

The conventional view holds that patients with oral cancer after operation have low risk of DVT. Lidders *et al.* (16) and Forouzanfar *et al.* (17), respectively, reported that the incidence of symptomatic VTE in patients after oral and maxillofacial surgery are 0.41% to 0.5%. However, since most VTE is non-symptomatic, the true incidence may be underestimated. Furthermore, with the development of ultrasound applications, asymptomatic DVT can be detected earlier. In our study, we found that the incidence of DVT in ICU patients was 33.6%, which was higher than that in the current research reports (15,18) of 11.9–26.3% in general wards. Compared with the non-DVT group, the preoperative GLU, postoperative D-dimer, and NLR were higher in the DVT group than in the non-DVT group, and we also found that the DVT group had longer MVT and LOS than the non-DVT group. The result of multivariate logistic analysis indicated that NLR level, preoperative GLU >5.15 mmol/L, and postoperative D-dimer >5.57 $\mu\text{g/mL}$ were independent risk factors of DVT in ICU patients with oral cancer, and the area under the curve (AUC) of NLR in predicting DVT was 0.729. We also assessed the correlation of the NLR level with the prognostic indicators, and the results showed that the NLR level was positively related with MVT ($r=0.36$; $P<0.001$) and LOS ($r=0.452$; $P<0.0001$).

The CRS has been shown to be an independent risk factor for thrombosis in patients with oral tumor (18). However, in our study, the CRS was not different between the DVT group and the non-DVT group, and the CRS' of both groups were higher than those reported by Kakei's *et al.* (18). The high CRS may be due to the peculiarities of the ICU, such as malignant conditions, severe illness, high APACHE II scores, advanced age, malnutrition, comorbidities, and confinement to bed after surgery.

There is a close link between inflammation and thrombosis (19); however, there are controversies surrounding the relationship of NLR and DVT. In patients after total joint arthroplasty (TJA), the preoperative NLR

Table 1 Clinical characteristics of the DVT and non-DVT groups

Variables	Non-DVT group (n=85)	DVT group (n=43)	P value
Age (years)	67.0 (59.8–79.0)	71.0 (62.5–79.25)	0.339
Gender (male/female)	57/28	25/18	0.321
BMI (kg/m ²)	21.44±3.9	22.53±4.0	0.146
Chemoradiotherapy history (no/yes)	75/10	36/7	0.477
Operation history (no/yes)	77/8	38/5	0.695
Diabetes history (no/yes)	69/16	36/7	0.723
Hypertension history (no/yes)	36/31	16/17	0.621
CHD history (no/yes)	71/14	37/6	0.711
Surgical variables			
Operative time (min)	355.0 (275.00–442.50)	360 (250.00–470.00)	0.998
Blood loss (mL)	300.0 (200.0–300.0)	300.0 (200.0–400.0)	0.771
Flap type (pedicle flap/free flap)	8/73	5/31	0.750
Preoperative laboratory data			
Hemoglobin (g/dL)	121.0±23.3	114.1±23.5	0.117
Activated partial thromboplastin time (s)	26.95 (25.40–29.30)	27.15 (25.02–30.00)	0.682
Albumin (g/dL)	36.55 (34.10–40.92)	36.35 (33.30–39.30)	0.201
Creatinine (mg/dL)	84.00 (66.75–97.50)	80.50 (68.25–99.00)	0.328
D-dimer (µg/mL)	0.66 (0.31–1.92)	1.11 (0.56–2.25)	0.093
TC (mmol/L)	4.75±1.22	5.05±1.27	0.218
TG (mmol/L)	1.07 (0.85–1.50)	1.16 (0.94–1.46)	0.491
HDL-C (mmol/L)	1.12±0.28	1.11±0.29	0.891
LDL-C (mmol/L)	3.02±0.90	3.26±0.91	0.176
GLU (mmol/L)	4.90 (4.58–5.90)	5.65 (4.90–7.23)	0.017*
Postoperative laboratory data			
Albumin (g/dL)	30.28±5.5	28.87±5.6	0.181
D-dimer (µg/mL)	3.64 (1.92–6.16)	5.81 (2.73–10.61)	0.009*
Anticoagulation therapy (no/yes)	43/42	20/23	0.663
APACHE II score	17.9±5.4	19.3±6.9	0.197
Charlson comorbidity index	1 (0–2)	1 (0–2)	0.924
CRS	12.0 (11.0–14.0)	12.5 (10.25–14.0)	0.360
MVT (days)	2.0 (1–3.75)	4.0 (2.0–6.0)	0.003*
LOS (days)	15.0 (12.0–19.0)	20.0 (18.0–25.0)	0.004*

Quantitative variables with a normal distribution were expressed as mean ± SD and with abnormal distribution were expressed as median (interquartile range). *, P<0.05. DVT, deep venous thrombosis; BMI, body mass index; CHD, coronary heart disease; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GLU, glucose; APACHE II, Acute Physiology and Chronic Health Evaluation II; CRS, Caprini Risk Score; MVT, mechanical ventilation time; LOS, length of stay.

Table 2 Comparison of the inflammatory and nutritional scores between non-DVT group and DVT group

Variables	Non-DVT group (n=85)	DVT group (n=43)	P value
NLR	2.54 (1.66–4.29)	4.60 (2.50–9.52)	<0.001*
PLR	164.10 (117.26–223.33)	173.85 (139.46–308.94)	0.067
PNI	36.25 (33.45–40.90)	36.89 (33.02–39.67)	0.828

Data were expressed as median (interquartile range). *, P<0.05. DVT, deep venous thrombosis; NLR, neutrophil to lymphocyte ratio; PLR, plate to lymphocyte ratio; PNI, prognostic nutritional index.

Table 3 Prediction of DVT, AUROC, and cut-off points

Variables	AUROC (95% CI)	Sensitivity	Specificity	Cut-off point
MVT (days)	0.64 (0.53–0.74)	0.615	0.631	2.5
Preoperative D-dimer (µg/mL)	0.59 (0.49–0.70)	0.513	0.667	1.03
Postoperative D-dimer (µg/mL)	0.65 (0.54–0.74)	0.538	0.741	5.57
GLU (mmol/L)	0.64 (0.53–0.74)	0.641	0.612	5.15

DVT, deep venous thrombosis; AUROC, area under the ROC curve; MVT, mechanical ventilation time; GLU, glucose; CI, confidence interval.

Table 4 Univariate and multivariate logistic regression analyses for DVT of patients with oral cancer after surgery in ICU

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
BMI (kg/m ²)	1.07 (0.97–1.18)	0.154	1.090 (0.963–1.232)	0.172
CRS	1.10 (0.93–1.30)	0.285	1.063 (0.868–1.301)	0.555
MVT (days)		0.005*		
≤2.5	1		1	
>2.5	2.981 (1.328–6.430)		1.854 (0.695–4.950)	0.218
Preoperative D-dimer (µg/mL)		0.053		
≤1.03	1		1	
>1.03	2.10 (0.99–4.44)		0.859 (0.311–2.378)	0.770
Postoperative D-dimer (µg/mL)		0.005*		
≤5.57	1		1	
>5.57	3.00 (1.39–6.48)		4.766 (1.765–112.874)	0.002*
GLU (mmol/L)		0.011*		
≤5.15	1		1	
>5.15	2.66 (1.25–5.67)		3.061 (1.147–8.163)	0.025*
NLR	1.259 (1.090–1.454)	0.002*	1.342 (1.130–1.594)	0.001*

*, P<0.05. DVT, deep venous thrombosis; ICU, intensive care unit; BMI, body mass index; CRS, Caprini Risk Score; MVT, mechanical ventilation time; GLU, glucose; NLR, neutrophil to lymphocyte ratio; OR, odds ratio; CI, confidence interval.

is significantly higher in the DVT group than in non-DVT group, but NLR cannot predict TJA-induced DVT accurately through ROC curve analysis (20). However, Barker *et al.* reported a link between NLR and DVT after total knee arthroplasty (TKA) with a positive conclusion (21), and recently Carobbio *et al.* (22) revealed that the risk of venous thrombosis is independently associated with NLR values ≥ 5 through multivariate analysis in polycythemia vera patients. Moreover, Kuplay *et al.* (23) found that patients with proximal DVT had a higher mean NLR than those with distal DVT. The study by Xing *et al.* (24) developed a practical nomogram based on NLR and PLR to accurately predict portal vein thrombosis in patients with liver cirrhosis. In our study, we found that the NLR was the

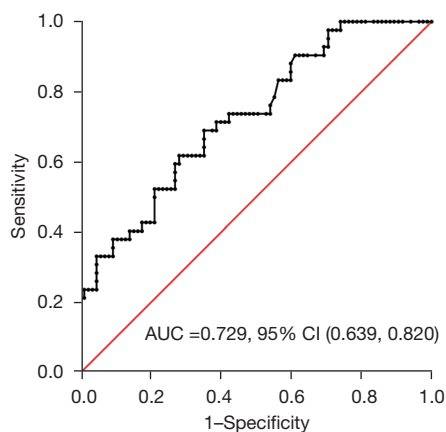


Figure 2 ROC curves for NLR in predicting DVT. AUC, area under the curve; ROC, receiver operating characteristic; NLR, neutrophil to lymphocyte ratio; DVT, deep venous thrombosis.

most significant difference among the three inflammatory and nutritional scores, and NLR was an independent risk factor of DVT (OR =1.342; P=0.001) and the AUC of NLR in predicting DVT was 0.729. Studies have found that the influence of NLR on DVT may be related to neutrophil activation and NETs formation (7,25,26).

Many studies have also indicated that NLR is of predictive value on the prognosis, especially for critical patients. Moisa *et al.* (27) reported that the NLR has the best independent predictive values for invasive mechanical ventilation need and death in critically ill coronavirus disease of 2019 (COVID-19) patients. Another study (28) indicated that NLR is increased in sepsis patients and is significantly correlated with sepsis severity evaluated by the sequential organ failure assessment (SOFA) score. The same study (28) indicated that NLR plays a role in prediction of severity and prognosis of patients with bloodstream infections (29) and is also predictive of a worse outcome of severe acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in frequent exacerbators with a cut-off value of 10.23 (30). In our study, we discovered that compared with the non-DVT group, the MVT and LOS were longer in the DVT group, moreover, the NLR level was positively related with MVT ($r=0.36$; $P<0.001$) and LOS ($r=0.452$; $P<0.0001$). Above all, these studies indicate that NLR is not only a risk factor of DVT, but also a valuable prognostic biomarker in critical patients.

We also found that postoperative D-dimer $>5.57 \mu\text{g/mL}$ was an independent risk factor of DVT. The causes of increased D-dimer include advanced age, tumor, surgical operation, infection, and so on. More importantly, D-dimer predicts significantly different overall survival rate in oral

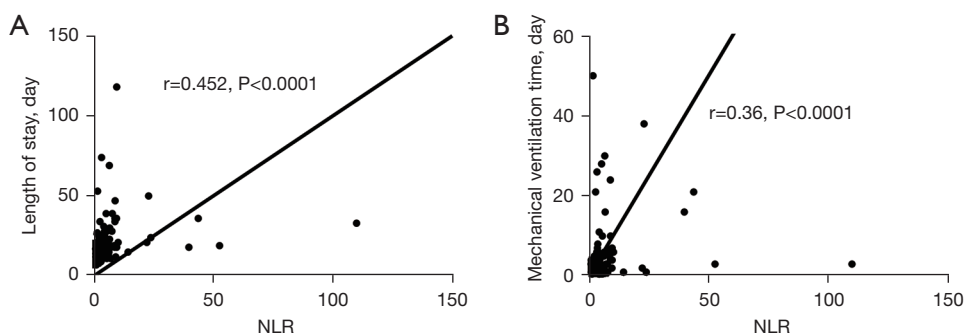


Figure 3 The correlation of NLR with LOS (A) and MVT (B). NLR, neutrophil to lymphocyte ratio; LOS, length of stay; MVT, mechanical ventilation time.

cancer patients with a cut-off value of 0.7 $\mu\text{g}/\text{mL}$ (31). A high preoperative D-dimer level in patients with oral squamous cell carcinoma suggests a poor prognosis, and the difference of D-dimer between preoperative and postoperative is related to the type of operation (32). In our present study, the difference of preoperative D-dimer between two groups was not different ($P=0.093$), but the postoperative D-dimer was different between the DVT group and non-DVT group ($P=0.009$), with no significant difference in the choice of surgical methods between the two groups ($P=0.75$). After multivariate logistical analysis, postoperative serum D-dimer level $>5.57 \mu\text{g}/\text{mL}$ was an independent risk factor of postoperative DVT, so when the postoperative serum D-dimer level is $>5.57 \mu\text{g}/\text{mL}$, the diagnosis of DVT should be confirmed as soon as possible.

Some surgical studies (33,34) have reported that perioperative hyperglycemia is a risk factor of DVT. In our present study, however, we focused on preoperative fasting blood GLU. First, we would like to predict high risk patients of postoperative DVT earlier. Second, due to the low basic blood GLU level of oral cancer patients (35), and the complicated operation, postoperative eating difficulties and other stress conditions, postoperative blood GLU level may be disturbed. In our study, it was an independent risk factor of DVT when the preoperative fasting blood GLU was over 5.15 mmol/L. As far as we know, this is the first report of this kind in the field of oral cancer.

Our study had several limitations. First, this was a retrospective study that was performed in a single center. Second, for a small number of patients, it was unclear whether DVT was present before surgery or not. A larger, prospective, multicenter study performed according to appropriate protocols is needed to validate our results.

In conclusion, this study showed that NLR level, preoperative GLU $>5.15 \text{ mmol}/\text{L}$, and postoperative D-dimer $>5.57 \mu\text{g}/\text{mL}$ were independent risk factors of DVT, and moreover, higher NLR level was related with longer MVT and LOS in ICU patients after oral cancer surgery. For patients admitted to the ICU after oral cancer surgery, immunity and nutrition status should be preoperatively improved, and fasting GLU should be preoperatively screened. This study can help us to identify these risk factors early, establish graded care early, and conduct early intervention.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-2453/rc>

Data Sharing Statement: Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-2453/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-2453/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional Ethics Committee of Sun Yat-sen Memorial Hospital (No. SYSEC-KY-KS-2021-188). Individual consent for this retrospective analysis was waived.

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