


# Diagnostic and Prognostic Value of Immune/Inflammation Biomarkers for Venous Thromboembolism: Is It Reliable for Clinical Practice?

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**Abstract:** Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), has been an important cause of sudden in-hospital death. Studies have shown that the immune/inflammatory response plays an important role in the pathogenesis of vascular disease, with representative markers in the blood including the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), systemic immune/inflammatory index (SII), etc. However, there is a variety of immune/inflammatory indicators. Moreover, most previous studies have been single-center investigations involving one or two indicators, with varying nature of cases, number of cases and study objectives, thereby making it difficult to reach consensus conclusions with good clinical guidelines. This article reviews the clinical value of immunoinflammatory indicators for VTE based on previous studies, including the diagnostic and prognostic capabilities. In conclusion, NLR provides promising predictive capability for the onset and prognosis of VTE and deserves extensive application in clinical practice. PLR also has certain diagnostic and prognostic value, but further studies are warranted to identify its reliability and stability. Monocytes, eosinophils and platelet-related indicators show some clinical association with VTE, although the predictive capabilities are mediocre. SII is of promising potential value for VTE and deserves further investigations. This review will provide new clues and valuable clinical guidance for the diagnosis and therapy of VTE.

**Keywords:** venous thromboembolism, immune/inflammation biomarker, diagnosis, prognosis

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), has been an important cause of sudden in-hospital death.<sup>1</sup> Until now, a number of risk factors have been identified to be associated with VTE, nevertheless, risk factors alone cannot promptly and effectively predict VTE occurrence and prognosis of mortality and therefore blood biomarkers are often required. The sensitivity of D-dimer for the diagnosis of VTE is sufficiently high for clinical practice. In contrast, the specificity of D-dimer is indeed suboptimal in clinical practice, as many pathophysiological processes may stimulate an increase in D-dimer. Recent studies have attempted to identify new biomarkers that balance sensitivity and specificity and act as a complement to D-dimers. Studies have shown that the immune/inflammatory response plays an important role in the pathogenesis of

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vascular disease, with representative markers in the blood including the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), systemic immune/inflammatory index (SII), etc.<sup>2–6</sup> These indicators are calculated from readily available biomarkers in the blood panel and are routinely measured. Over the past decades, the clinical value of these indicators of immune/inflammatory response for VTE has gradually become one of the hot topics of research, as reflected not only by the increasing number of studies published by researchers from different countries over the years, as well as their impact. (Figure 1) These studies have identified and confirmed the clinical value of these inexpensive and readily available indicators in the diagnosis and prognosis of mortality in VTE, helping to improve the specificity of VTE detection and suggesting high-risk factors for poor prognosis. However, there is a variety of immune/inflammatory indicators. Moreover, most previous studies have been single-center investigations involving one or two indicators, with varying nature of cases, number of cases and study objectives, thereby making it difficult to reach consensus conclusions with good clinical guidelines. Therefore, there is still a need for multicenter prospective studies to further verify the clinical value of different immune/inflammatory indicators. This article reviews the clinical value of immune/inflammatory indicators for VTE based on previous studies, including the diagnostic and prognostic capabilities, that will provide new clues and valuable clinical guidance for the diagnosis and therapy of VTE.

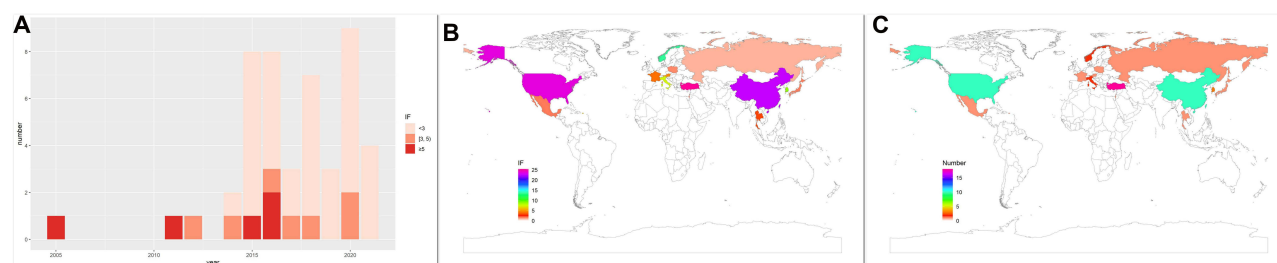
We systematically searched PubMed, Embase, and Web of Science for relevant literature up to June 2021. The search terms used to search literature were as followed: (“neutrophil/lymphocyte ratio” OR “neutrophil to lymphocyte ratio” OR “NLR”) OR (“platelet/lymphocyte ratio” OR “platelet to lymphocyte ratio” OR “PLR”) OR (“monocyte/lymphocyte ratio” OR “MLR” OR “lymphocyte/monocyte ratio” OR

“LMR”) OR (“systemic immune/inflammatory index” OR “SII”) OR (eosinophils) OR (platelets) AND (“pulmonary embolism” OR “PE”) OR (“deep venous thrombosis” OR “DVT”) OR (“venous thromboembolism” OR “VTE”). In addition, related articles and the references in the relevant studies were manually screened for additional eligible studies. The studies were included if they met the following criteria: 1) patients in the studies were diagnosed PE or DVT or VTE; 2) studies reported the specificity/sensitivity/cutoff value of immune/inflammatory indicators; 3) studies assessed associations between immune/inflammatory indicators and diagnosis/prognosis. The studies were excluded if they met the following criteria: 1) studies were not available of sufficient data; 2) studies were abstracts, letters, editorials, expert opinion, case reports; 3) studies were non-clinical or non-human research.

## NLR and VTE

There are a number of studies on the clinical value of NLR in VTE. (Table 1) Logistic regression analysis and COX regression analysis have shown that NLR has good diagnostic value and prognostic capability for VTE. The receiver operating characteristic curve (ROC) analysis results are displayed in Figure 2A.

NLR provides some clinical diagnostic value for acute pulmonary embolism (APE). Ates et al identified NLR as an independent predictor of massive APE in 639 patients with an odds ratio (OR) of 2.22.<sup>7</sup> ROC analysis determined that NLR had good clinical diagnostic value for massive APE (AUC=0.893,  $p<0.001$ ). Ateş et al also demonstrated a comparison of 34 patients with pulmonary embolism (PE) and 38 patients with community-acquired pneumonia (CAP) and found that patients with PE had lower levels of NLR on both the day of admission and the third day of admission ( $p=0.002$ ,  $p=0.004$ ).<sup>8</sup> The NLR/D-dimer ratio provided better differential diagnostic power



**Figure 1** (A) The number of studies on immune/inflammation biomarkers in VTE increased dramatically from 2005 to 2021. (B) A number of researchers around the world have published numerous research findings in this area, among which American researchers have published papers with the highest impact factors. (C) Studies on immune/inflammation biomarkers are conducted in various countries, among which Turkish researchers have reported the most.

Table 1 Studies of NLR for VTE

Study	Year	Country	Study Design	Number of Individuals	Age (Years)	VTE Type	Follow Up	Outcomes	NLR Cut-Off	Sensitivity (%)	Specificity (%)	AUC	OR/HR and p value
Duman et al <sup>21</sup>	2021	Turkey	Retrospective	828	62 (51–73) <sup>b</sup>	PE	12 months	30-day /6-month/ 12-month mortality	6.1 / 3.25 / 3.14	75/71.4/68.6	75.6/60.7/ 59.8	0.75/ 0.71/ 0.67	HR=13.8/2.77/2.0, p=0.001/ 0.001/0.003
Bi et al <sup>13</sup>	2021	China	Retrospective	72	60.10 ±0.99 <sup>a</sup> (High-risk) 59.23 ±0.87 <sup>a</sup> (Moderate-risk) 59.26 ±0.82 <sup>a</sup> (Low-risk)	APE	NA	Mortality	NA	77.9	89	0.861	NA
Go et al <sup>36</sup>	2021	Republic of Korea	Retrospective	114	69 (35–84) <sup>b</sup>	DVT	NA	Mortality	NA	NA	NA	NA	HR=1.324, p=0.428
Peng et al <sup>31</sup>	2021	China	Retrospective	52	75.67 ±8.48 <sup>a</sup>	VTE	In hospital	Probability of VTE	NA	NA	NA	NA	OR=2.003, p=0.078
Köse et al <sup>9</sup>	2020	Turkey	Retrospective	103	67.6±13.1 <sup>a</sup>	PE	39 months	Probability of PE and long-term mortality	NA	NA	NA	NA	OR:1.52, p<0.001; HR:1.17, p=0.003 (Moderate-low and low risk PE); HR:0.99, p=0.859 (Moderate-high and high risk PE)
Liu et al <sup>17</sup>	2020	China	Retrospective	101	64.00 (57.50–71.00) <sup>b</sup>	PAPE	30 days	30-day mortality	12	62.5	90.9	0.823	OR=1.171, p=0.000
Phan et al <sup>20</sup>	2020	USA	Retrospective	191	59.5±16.0 <sup>a</sup> (survived), 62.3 ±15.2 <sup>a</sup> (died)	APE	In hospital	All-cause and In-hospital mortality	5.46	75	66.9	0.692	NA, p<0.01

(Continued)

Table 1 (Continued).

Study	Year	Country	Study Design	Number of Individuals	Age (Years)	VTE Type	Follow Up	Outcomes	NLR Cut-Off	Sensitivity (%)	Specificity (%)	AUC	OR/HR and p value
Ghaffari et al <sup>23</sup>	2020	USA	Retrospective	492	62.1 ± 17.2 <sup>a</sup>	APE	12 months	Mortality	NA	NA	NA	NA	NA, p=0.206
Kasapoğlu et al <sup>14</sup>	2019	Turkey	Retrospective	550	68 (19–86) <sup>b</sup>	APE	30 days	30-day mortality	7.3	69	48	0.604	HR=1.27, p=0.669; HR=1.27, p=0.669 (subgroup without comorbidities)
Telo et al <sup>19</sup>	2019	Turkey	Retrospective	82	61.18 ± 15.51 <sup>a</sup>	APE	30 days	In-hospital mortality and 30-day mortality	3.56	66	53	0.675	NA
Farah et al <sup>25</sup>	2019	Israel	Retrospective	272	62 ± 18.9 <sup>a</sup>	Acute VTE	NA	Probability of acute VTE	5.3	69	57	0.67	OR=1.2, p=0.041
Seo et al <sup>29</sup>	2019	South Korea	Retrospective	102	69.8 ± 7.9 <sup>a</sup>	VTE	In hospital	Probability of acute VTE	1.9	57.8	55.6	0.589	OR=1.95, p=0.013
Ertem et al <sup>24</sup>	2018	Turkey	Retrospective	294	67.21 ± 14.74 <sup>a</sup>	APE	30 days	In-hospital mortality and 30-day mortality	NA	NA	NA	NA	HR:0.990, p=0.240
Grilz et al <sup>33</sup>	2018	Austria	Retrospective	128	62 (50–68) <sup>b</sup>	VTE	24 months	Probability of VTE and 24-month mortality	5.7	NA	NA	NA	HR=1.2, p=0.049
Fuentes et al <sup>48</sup>	2018	USA	Retrospective	13	58 (51–64) <sup>b</sup>	VTE	21.3 months	Probability of acute VTE	NA	46.2	47.5	0.47	HR=0.8, p=0.8
Artoni et al <sup>26</sup>	2018	Italy	Retrospective	486	47.9 ± 16.1 <sup>a</sup>	VTE	NA	Probability of acute VTE	NA	NA	NA	NA	OR=0.69, p>0.05

Yao et al <sup>28</sup>	2018	China	Retrospective	120	64.1 ± 13.2 <sup>a</sup>	DVT	In hospital	Probability of acute DVT	NA	NA	NA	0.533, 0.613	OR=1.11, p<0.035 (preoperative NLR), OR=1.20, p<0.001 (postoperative NLR)
Jia et al <sup>18</sup>	2017	China	Retrospective	154	62.54 ± 16.90 <sup>a</sup> (survived), 56.60 ± 14.80 <sup>a</sup> (died)	APE	30 days	30-day mortality	7.03	83.3	75.6	0.803	NA
Ming et al <sup>34</sup>	2017	China	Retrospective	115	52.17 ± 14.13 <sup>a</sup>	Acute DVT	NA	Probability of acute DVT	1.76	83.5	41	0.82	OR=1.889, p=0.024
Ateş et al <sup>8</sup>	2017	Turkey	Retrospective	34	64.1 ± 15.8 <sup>a</sup>	APE	In hospital	Probability of PE	NA	NA	NA	0.893	OR:2.22, p<0.001 (massive APE)
Mehmet Karataş et al <sup>22</sup>	2016	Turkey	Retrospective	203	65.8 ± 18.1 <sup>a</sup>	APE	20 months	30-day mortality and long-term mortality	NA	NA	NA	NA	HR=1.13, p=0.01
Ma et al <sup>16</sup>	2016	China	Retrospective	248	66 (52–74, survived) <sup>b</sup> , 75 (65–83, died) <sup>b</sup>	APE	30 days	30-day mortality	5.99	80	66.7	0.779	OR = 1.13, p=0.003
Grimnes et al <sup>32</sup>	2016	Norway	Retrospective	25,107	48.4 ± 17.2 <sup>a</sup>	VTE	9.95 years	Probability of VTE and Mortality	NA	NA	NA	NA	HR=2.36, p=0.21; HR=2.13, p=0.02
Celik et al <sup>10</sup>	2015	Turkey	Retrospective	112	59 ± 16 <sup>a</sup>	APE	In hospital	Probability of PE	NA	NA	NA	NA	OR=0.887, p=0.068
Barker et al <sup>30</sup>	2015	USA	Retrospective	10	65 ± 5 <sup>a</sup>	VTE	In hospital	Probability of acute VTE	NA	NA	NA	NA	OR=1.38, p=0.02

(Continued)

Table 1 (Continued).

Study	Year	Country	Study Design	Number of Individuals	Age (Years)	VTE Type	Follow Up	Outcomes	NLR Cut-Off	Sensitivity (%)	Specificity (%)	AUC	OR/HR and p value
Bakirci et al <sup>40</sup>	2015	Turkey	Retrospective	77	53.7±10.2 <sup>a</sup>	VTE	In hospital	Probability of acute VTE	1.84	88.2	67.6	0.849	NA
Soylu et al <sup>12</sup>	2014	Turkey	Retrospective	142	58.9±14.5 <sup>a</sup>	APE	In hospital	In-hospital mortality	5.7	81	71	0.697	OR = 10.8, p=0.019
Akgülü et al <sup>11</sup>	2014	Turkey	Retrospective	206	61.8±11.8 <sup>a</sup>	APE	3.0 (2.0–5.0) days	Early mortality	8.4	76.67	81.82	0.825	OR = 1.079, p=0.037
Ferroni et al <sup>35</sup>	2014	Italy	Retrospective	55	NA	DVT	9 months	Probability of acute DVT	3	59	57	0.55	HR=2.5, p=0.06
Kayrak et al <sup>15</sup>	2013	Turkey	Retrospective	359	62±16 <sup>a</sup> (survived), 73±10 <sup>a</sup> (died)	APE	30 days	30-day mortality	9.2	68.6	80.5	NA	HR=1.03, p=0.008

Notes: <sup>a</sup>Mean±standard deviation; <sup>b</sup>Interquartile range.

Abbreviations: PE, pulmonary embolism; APE, acute pulmonary embolism; PAPE, postoperative acute pulmonary embolism; DVT, deep venous thrombosis; VTE, venous thromboembolism; NA, not available; HR, hazard ratio; OR, odds ratio.

between PE and CAP than traditional indicators such as D-dimer, PCT and CRP, with a sensitivity of 97.4%, a negative predictive value of 96.7% and a positive predictive value of 91.7%, and an AUC of 0.921. Köse et al also observed in 103 patients with PE that NLR was significantly associated with the onset of PE (OR=1.52,  $p<0.001$ ).<sup>9</sup> Furthermore, NLR was strongly associated with the prognosis of mortality in low-medium risk PE and low risk PE (hazard ratio [HR]=1.17,  $p=0.033$ ), while NLR was not associated with the prognosis of mortality in medium-high risk PE and high risk PE (HR=0.99,  $p=0.859$ ). Celik et al identified significantly higher NLR levels in patients with acute PE than in those with non-acute PE ( $6.2\pm 2.9$  vs  $5.4\pm 3.0$ ,  $p=0.03$ ) and a high positive correlation between NLR and PLR ( $r=0.488$ ,  $p<0.001$ ).<sup>10</sup> However, regression analysis showed that NLR did not predict the onset of acute PE (OR=0.887,  $p=0.068$ ).

NLR is strongly correlated with in-hospital mortality, 30-day mortality and overall mortality in patients with PE. Akgüllü et al observed in 206 patients with APE that NLR was associated with early mortality (OR=1.079, 95% CI:1.005–1.160).<sup>11</sup> ROC analysis showed that NLR had favorable prognostic value with a sensitivity of 76.67%, a specificity of 81.82% and an AUC of 0.825. In addition, NLR showed a higher sensitivity (90%), specificity (79.55%) and AUC (0.906) when combined with sPESI. In 142 patients with APE, Soylu et al have found that the group with a high NLR ( $\geq 4.4$ ) was more likely to have massive PE (66.2% vs 36.6%,  $P<0.001$ ) than the group with a low NLR ( $<4.4$ ), and its in-hospital mortality (21.1% vs 1.4%,  $P<0.001$ ) was also higher.<sup>12</sup> Multivariate regression analysis identified NLR as an independent predictor of in-hospital mortality, and ROC analysis showed that patients with an NLR value over 5.7 had a 10.8-fold higher mortality rate than those with an NLR value below 5.7. Bi et al found that NLR was significantly higher in the patients who died than in the survival group ( $P<0.05$ ) in 72 patients with PE. The AUC for NLR to predict mortality was 0.861, with a sensitivity of 0.779 and specificity of 0.890.<sup>13</sup> And a combination of NLR with BNP, TnI and D-dimer showed a higher predictive value with an AUC of 0.92, sensitivity of 0.889 and specificity of 0.904.

Kasapoğlu et al retrospectively analysed 550 patients with APE, where NLR levels were significantly higher in patients who died within 30 days ( $p=0.003$ ).<sup>14</sup> Short-term mortality was also notably higher in patients with NLR  $>7.3$  ( $p<0.05$ ). Although Cox regression analysis found

that NLR was not an independent predictor of death for overall patients (HR=1.27,  $p=0.669$ ). A subgroup analysis in patients without comorbidities showed that NLR was an independent predictor of mortality (HR=3.3,  $p=0.016$ ). Kayrak et al performed multivariate Cox regression analysis on 359 patients with APE and found that NLR was an independent predictor of 30-day mortality (HR=1.03, 95% CI:1.01–1.06,  $p=0.008$ ) with a cut-off value of 9.2 and sensitivity, specificity, negative predictive value and positive predictive value of 68.6%, 80.5%, 93.9% and 36.5%, respectively.<sup>15</sup> Ma et al also found in 248 patients with APE that a 1 unit increase of NLR was associated with a 13% increased risk of death at 30 days (OR=1.13, 95% CI:1.04–1.23,  $p=0.003$ ).<sup>16</sup> NLR predicted 30-day mortality with a sensitivity of 80%, specificity of 66.7% and AUC of 0.79 (95% CI: 0.703–0.880).

Liu et al found that 24 patients (23.8%) died within 30 days in 101 patients with postoperative acute pulmonary embolism (PAPE).<sup>17</sup> Multivariate analysis showed that NLR was an independent predictor of 30-day mortality in patients with PAPE, with a 1-unit increase in NLR related to a 17.1% increase in the probability of death (OR=1.171, 95% CI:1.073–1.277,  $p=0.000$ ). ROC analysis showed that NLR had a predictive sensitivity of 62.5%, specificity of 90.9% and AUC of 0.823. Jia et al detected significantly higher levels of NLR in 154 APE patients with right heart insufficiency and regression analysis showed that NLR was associated with right heart insufficiency (OR=1.075,  $p=0.024$ ).<sup>18</sup> Besides, NLR was associated with 30-day mortality ( $P<0.001$ ) with a predictive sensitivity of 83.3%, specificity of 75.6% and AUC of 0.803 (95% CI: 0.730–0.875).

NLR has also been verified to predict the mortality when risk levels are stratified for PE patients. Telo et al revealed that NLR was significantly higher in PE patients with high-risk for mortality than in those with low-risk for mortality based on the sPESI score ( $p<0.01$ ).<sup>19</sup> NLR had a predictive sensitivity of 66%, a specificity of 53% and an AUC of 0.675 (95% CI: 0.556–0.794). All patients were divided into two groups according to the NLR cut-off value of 3.56, showing statistically significant increase in-hospital mortality, 3rd month mortality and overall 3-month mortality in the groups above 3.56 ( $\chi^2=4.771$ ,  $p<0.05$ ;  $\chi^2=4.383$ ,  $p<0.05$ ;  $\chi^2=9.101$ ,  $p<0.01$ ). Phan et al found there was no difference in NLR levels among 191 APE patients with low-risk, sub-risk and high-risk for mortality ( $p=0.58$ ).<sup>20</sup> However, NLR was significantly higher in patients who died than in those who survived



(8.10 [4.28–13.7] vs 3.91 [2.46–6.71];  $p < 0.01$ ). Furthermore, elevated NLR was associated with all-cause mortality with a predictive sensitivity of 75.0%, specificity of 66.9% and AUC of 0.692 (95% CI: 0.568–0.816).

Duman et al found that an NLR above 6.1 increased mortality at 30 days by 13.8-fold in a cohort of 828 PE patients.<sup>21</sup> NLR over 3.25 was an independent risk factor for 6-month mortality (HR=2.77, 95% CI: 1.48–5.18,  $p=0.001$ ) and NLR over 3.14 was an independent risk factor for 1-year mortality (HR=2.20, 95% CI: 1.32–3.66,  $p=0.003$ ). Karataş et al followed 203 patients with APE for a mean of 20 months and 34 patients (17%) died during the follow-up period.<sup>22</sup> Patients who died within 30 days had significantly higher NLR levels than those who survived (9.9 vs 4.5,  $p=0.01$ ). NLR levels were also markedly elevated during long-term follow-up (8.4 vs 4.1,  $p=0.01$ ). Cox regression analysis also demonstrated elevated NLR was an independent risk factor for overall mortality (HR = 1.13, 95% CI: 1.04–1.23,  $p=0.01$ ).

However, a few studies have shown that there is no significant correlation between NLR and death in patients with PE. For example, Ghaffari et al found no significant difference in NLR in 492 APE patients with and without major cardiopulmonary adverse events ( $p=0.206$ ) and that NLR was not associated with patient mortality.<sup>23</sup> Ertem et al followed 294 patients with APE, of whom 64 (21.8%) died and 230 (78.2%) survived.<sup>24</sup> Although NLR was higher in patients who died ( $P < 0.001$ ), there was no significant correlation between NLR and death (HR: 0.990,  $P=0.240$ ).

Meaningful findings regarding NLR have also been obtained when some investigators have analysed PE and DVT together as VTE. Farah et al discovered significantly elevated NLR level in 272 patients with acute VTE ( $p < 0.001$ ).<sup>25</sup> Multivariate logistic regression models identified NLR for early detection of potential acute VTE (OR=1.2, 95% CI: 1.01–1.4,  $p=0.041$ ), with a predictive sensitivity of 69%, specificity of 57% and AUC of 0.67 (95% CI: 0.60–0.75). However, Artoni et al observed no increment in the risk of VTE in patients with high NLR among 486 patients (OR=0.69, 95% CI: 0.34–1.39).<sup>26</sup> Fuentes et al identified 13 patients (11.6%) with VTE during follow-up of 112 gastric cancer patients, but NLR was not associated with the onset of VTE (HR=0.8,  $p=0.8$ ), with a sensitivity of 46.2% and specificity of 47.5%.<sup>27</sup>

NLR can also predict the occurrence of VTE after osteopathic surgery. Yao et al found that 120 patients

who suffered postoperative DVT (16.4%) had a significantly higher preoperative NLR ( $p=0.030$ ) and postoperative NLR ( $p=0.015$ ) than those who did not suffer from DVT among 733 patients after total joint arthroplasty.<sup>28</sup> Multiple logistic regression analysis showed that both preoperative NLR (OR=1.11,  $P < 0.035$ ) and postoperative NLR (OR=1.20,  $P < 0.001$ ) were independently associated with the occurrence of DVT, with an AUC of 0.533 (95% CI: 0.473–0.592) and an AUC of 0.613 (95% CI: 0.564–0.662), respectively. Seo et al observed that VTE occurred in 102 cases (38.6%) at 1 week postoperatively in 264 patients after total knee arthroplasty.<sup>29</sup> Preoperative NLR  $\geq 1.90$  was the only independent predictor of postoperative VTE (OR=1.95, 95% CI: 1.16–3.31,  $p=0.013$ ). ROC analysis revealed a predictive sensitivity of 57.8%, specificity of 55.6% and AUC of 0.589. Barker et al demonstrated higher levels of NLR in patients with total knee arthroplasty than in patients with unicompartmental knee arthroplasty ( $p=0.02$ ).<sup>30</sup> NLR could predict VTE during hospitalization in patients after total knee arthroplasty (OR=1.38; 95% CI: 1.05–1.80,  $p=0.02$ ). However, Peng et al found that NLR was not an independent predictor of VTE after hip fracture among 52 patients over 60 years old, although the NLR was higher in them than in those without VTE ( $p=0.078$ ).<sup>31</sup>

NLR was also correlated with death in patients with VTE. Grimnes et al found although NLR was not associated with first occurrence or recurrence of VTE, NLR was associated with increased mortality in 25,107 patients (HR=2.13, 95% CI: 1.26–3.58,  $p=0.02$ ).<sup>32</sup> Grilz et al identified 128 (16.4%) patients who experienced VTE during follow-up of 1469 cancer patients, and NLR was statistically associated with the occurrence of VTE after multivariate adjustment for age, gender and cancer stage (HR=1.2, 95% CI: 1.0–1.4,  $p=0.049$ ).<sup>33</sup> In addition, NLR was associated with 24-month mortality with a HR of 1.5 (95% CI: 1.0–1.4,  $p < 0.001$ ). Ming et al also observed that NLR was an independent risk factor for death in 115 patients with acute DVT (OR=1.889, 95% CI: 1.086–3.286,  $p=0.024$ ).<sup>34</sup> However, Ferroni et al revealed from 55 cancer patients receiving chemotherapy that symptomatic VTE patients had higher post-chemotherapy NLRs than pre-chemotherapy NLRs ( $p=0.015$ ).<sup>35</sup> NLR  $> 3$  was associated with the incidence of symptomatic VTE, with an HR of 2.5 (95% CI: 1.0–6.4,  $p=0.06$ ). And patients with NLR  $> 3$  had a worse survival rate at one year (Log rank test: 2.32,  $p = 0.020$ ). Although ROC analysis showed a sensitivity of 59%, specificity of 57% and AUC of



0.55, NLR was not an independent risk factor for the occurrence of VTE ( $p>0.05$ ). Go et al found that among 114 lung cancer patients with VTE, those with high NLR responded poorly to anticoagulation therapy ( $p=0.004$ ).<sup>36</sup> Moreover, NLR was associated with prognosis of mortality in lung cancer patients with VTE, but NLR did not predict mortality ( $p>0.05$ ).

NLR may have an association with endothelial cell function and pulmonary hypertension. In a study of 106 patients with chronic thromboembolic pulmonary hypertension, Yanartas et al found that patients with higher NLR on admission experienced significantly higher mortality and NLR was an independent predictor of death ( $OR=2.767$ ,  $p=0.002$ ).<sup>37</sup> ROC analysis showed an optimal cut-off value of 2.54 for NLR, with a sensitivity of 86%, specificity of 40%, and AUC of 0.825. Correlation analysis also showed a clear correlation between NLR and preoperative pulmonary vascular resistance ( $r=0.214$ ,  $p=0.027$ ). Kurtipek et al observed significantly higher NLR values in the 71 patients with APE than in healthy controls ( $4.2\pm 4.90$  vs  $1.89\pm 1.46$ ,  $p=0.0001$ ), suggesting possible endothelial cell dysfunction.<sup>38</sup>

NLR can also indicate the location of venous thrombosis in the lower extremities. Kuplay et al found that NLR correlated with thrombus location in 933 patients with DVT.<sup>39</sup> Mean NLR was higher in patients with proximal DVT than distal DVT ( $4.40\pm 4.28$  vs  $3.54\pm 3.55$ ;  $p<0.05$ ) and NLR was increased with the number of venous segments involved ( $p<0.001$ ). Its predictive sensitivity was 65.4% and specificity 55.0%, with an AUC of 0.6 (95% CI: 0.56–0.64). Bakirci et al identified significant differences in NLR between patients with PE, proximal DVT and distal DVT in 77 patients ( $p<0.001$ ).<sup>40</sup> An  $NLR>1.84$  predicted VTE with a sensitivity of 88.2%, specificity of 67.6% and AUC of 0.849 (95% CI: 0.765–0.913,  $p<0.001$ ).

NLR may be related to iliac vein stent occlusion. Jahangiri et al observed higher NLR level in patients with early stent occlusion ( $p=0.026$ ) in 50 patients with iliac vein stent placement.<sup>41</sup> However, COX analysis showed that NLR was not an independent predictor of stent occlusion and only had borderline significance ( $p=0.050$ ,  $HR=12.19$ , 95% CI: 1–147.85).

Interesting results can also be obtained when an analysis is performed on neutrophil counts alone. Kushnir et al have found that an elevated neutrophil count is associated with an increasing risk of venous thrombosis in 43,538 outpatients and that neutrophilia may be a marker of

vulnerability to VTE.<sup>42</sup> A neutrophil count  $\geq 7.8 \times 10^9/L$  was not significantly associated with the development of VTE. Patients with a neutrophil count  $\geq 9.0 \times 10^9/L$  had a twofold increased risk of VTE ( $OR=2.0$ , 95% CI: 1.3–3.1,  $p=0.003$ ). Patients with a neutrophil count  $\geq 10.0 \times 10^9/L$  had a higher risk of VTE ( $OR=2.3$ , 95% CI: 1.2–4.8,  $p=0.019$ ).

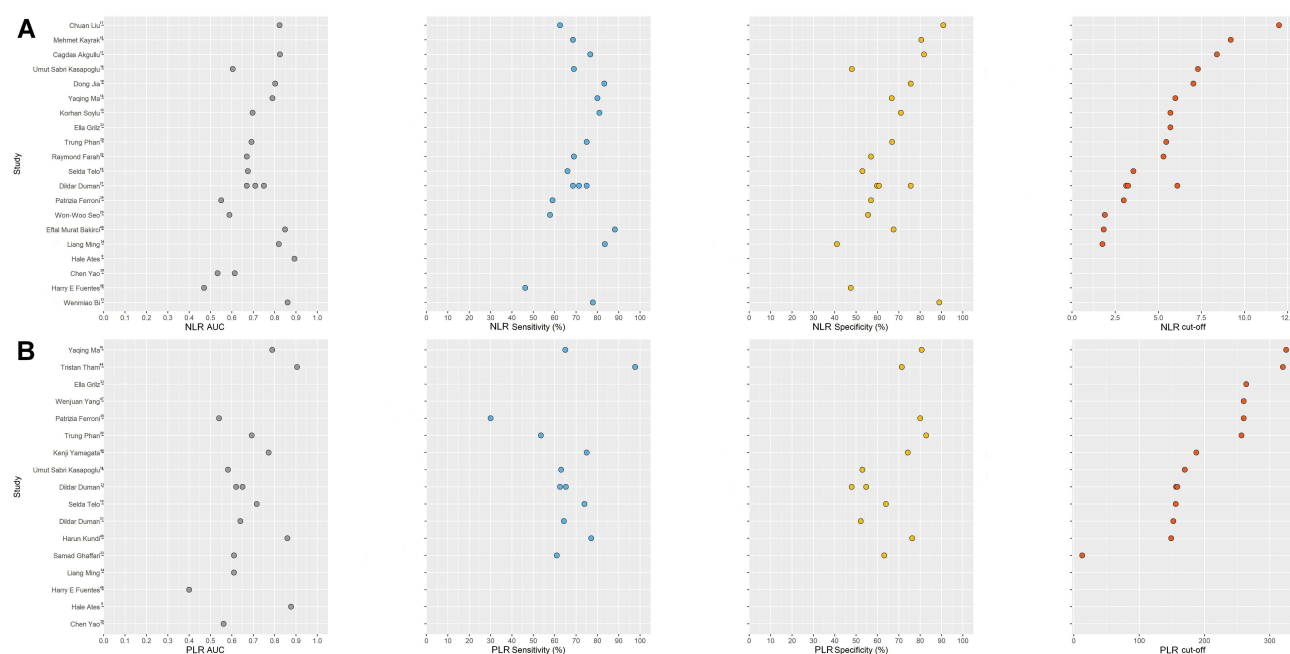
In patients with corona virus disease 2019 (COVID-19), elevated NLR may increase the risk of VTE development. Mareev et al observed a 2.5-fold increase in NLR levels when high-dose glucocorticoid (GCS) pulse therapy was administered to patients with novel coronavirus pneumonia ( $p=0.006$ ), and the increase was significantly correlated with D-dimer ( $r=0.49$ ,  $p=0.04$ ).<sup>43</sup> The authors suggested that therapy with high doses of GCS exerted a rapid anti-inflammatory effect, but also elevated NLR and D-dimer levels, increasing the risk of VTE.

NLR also has a predictive value for the prognosis of mortality in patients with portal vein/hepatic vein tumour thrombosis (PVTT/HVTT). Li et al found that preoperative NLR was a prognostic predictor after hepatic resection in 81 patients with PVTT/HVTT.<sup>44</sup> The median overall survival (OS) and disease-free survival (DFS) were significantly shorter in the high NLR ( $>2.9$ ) group than in the low NLR group (OS: 6.2 months vs 15.7 months,  $p=0.007$ ; DFS: 2.2 months vs 3.7 months,  $p=0.039$ ).  $NLR>2.9$  was considered an independent predictor of prognosis of mortality ( $p=0.034$ ,  $HR=1.866$ , 95% CI: 1.048–3.322). There was also a significant positive correlation between NLR and Child-Pugh score ( $r=0.276$ ,  $p=0.015$ ) and the maximum diameter of the tumour ( $r=0.435$ ,  $p<0.001$ ).

## PLR and VTE

PLR has certain diagnostic value for the onset of APE and is associated with in-hospital mortality, 30-day mortality and overall mortality (Table 2). ROC analysis results for PLR are displayed in Figure 2B. Ates et al identified PLR ( $OR=1.59$ ,  $p<0.001$ ) as an independent predictor of massive APE in 639 patients.<sup>7</sup> ROC analysis provided good differential diagnostic value of PLR for massive APE with an AUC of 0.877 ( $p<0.001$ ). However, Celik et al found that PLR was not an independent predictor of APE in 112 patients ( $OR=0.998$ ,  $p=0.340$ ).<sup>10</sup>

Ghaffari et al did not find a difference in PLR between patients with and without major cardiopulmonary adverse events in 492 patients with APE ( $p=0.338$ ), but PLR was associated with in-hospital mortality ( $p<0.01$ ) with a sensitivity of 61%, specificity of 63.2% and AUC of



**Figure 2 (A)** The AUC of NLR ranged from 0.47 to 0.893, the sensitivity from 46.2% to 88.2%, the specificity from 41% to 90.9%, and the cutoff value from 1.76 to 12, indicating that NLR provide promising predictive capability for VTE, but the results varied between studies. **(B)** The AUC of PLR ranged from 0.4 to 0.905, the sensitivity from 30% to 97.66%, the specificity from 47.9% to 82.8%, and the cutoff value from 12.8 to 325, indicating that PLR has certain predictive value for VTE, whereas the results also varied between studies.

0.61 (95% CI: 0.50, 0.72).<sup>23</sup> Karataş et al observed significantly higher levels of PLR in 203 patients with APE who died within 30 days ( $n=14$ ,  $p=0.01$ ), as well as in long-term follow-up ( $n=20$ ,  $p=0.01$ ).<sup>15</sup> Elevated PLR levels were independently associated with total mortality with a HR of 1.002 (95% CI: 1.001–1.004,  $p=0.01$ ).

PLR could also predict prognosis of mortality in subgroups of patients with different risks of PE. Köse et al found that PLR was associated with prognosis of mortality in patients with moderate-high risk PE (HR=1.01,  $p=0.046$ ) while not with prognosis of mortality in patients with low risk and moderate-low risk PE (HR=1.0,  $p=0.545$ ) among 103 patients.<sup>9</sup> Phan et al identified no difference in PLR between low-risk, sub-risk and high-risk for mortality in 191 PE patients ( $p=0.02$ ).<sup>20</sup> However, patients who died had significantly higher PLR levels (263 vs 148;  $p<0.01$ ) and elevated PLR was associated with all-cause mortality with a sensitivity of 53.6%, specificity of 82.8% and AUC of 0.693 (95% CI: 0.580–0.805,  $p<0.01$ ). Telo et al observed a statistically significant increase in PLR in patients with high-risk for mortality compared to those with low-risk for mortality according to the sPESI score ( $p<0.01$ ).<sup>19</sup> And ROC analysis showed that PLR was associated with total mortality at 3rd month (OR=6.325,  $p<0.01$ ) with a sensitivity of 74%, specificity of 64% and

an AUC of 0.717 (95% CI: 0.539–0.896). Among 646 patients with APE, Kundi et al found higher levels of PLR in patients with high sPESI scores ( $p<0.001$ ).<sup>45</sup> PLR was independently associated with in-hospital mortality in patients with APE ( $p<0.001$ ) with a sensitivity of 77.1%, a specificity of 76.3% and an AUC of 0.860 (95% CI: 0.50, 0.72).

However, several more studies have also found that PLR could not predict death in PE patients, either at 30 days or in the long term. Kasapoğlu et al discovered a significantly higher level of PLR in APE patients who died within 30 days ( $p=0.022$ ) and a significantly higher short-term mortality in patients with PLR>170.<sup>14</sup> However, Cox regression analysis showed that PLR was not an independent risk factor for APE mortality (HR=1.4,  $p=0.503$ ). Ma et al observed a higher PLR ( $p<0.01$ ) in 248 APE patients who died, which was associated with short-term mortality (OR:1.002, 95% CI: 0.997–1.008,  $p=0.003$ ).<sup>16</sup> But PLR was not an independent predictor of overall mortality. Jia et al also found significantly higher levels of PLR in APE patients with right heart insufficiency ( $p=0.041$ ).<sup>18</sup> While there was no significant difference in PLR levels between dead and surviving patients ( $p=0.246$ ), and regression analysis showed that PLR was not associated with 30-day mortality ( $p>0.05$ ).

Table 2 Studies of PLR for VTE

Study	Year	Country	Study Design	Number of Individuals	Age (Years)	VTE Type	Follow Up	Outcomes	PLR Cut-Off	Sensitivity (%)	Specificity (%)	AUC	OR/HR and p value
Duman et al <sup>21</sup>	2021	Turkey	Retrospective	828	62 (51–73) <sup>b</sup>	PE	12 months	30-day /6-month/ 12-month mortality	158.38/ 156.38/ 152.38	62.5/65.3/ 64.3	47.9/54.8/ 52.2	0.62/ 0.65/ 0.64	NA
Peng et al <sup>31</sup>	2021	China	Retrospective	52	75.67 ±8.48 <sup>a</sup>	VTE	In hospital	Probability of VTE	NA	NA	NA	NA	NA, p=0.051
Yamagata et al <sup>46</sup>	2021	Japan	Retrospective	101	72 (29–93) <sup>b</sup>	VTE	In hospital	Probability of acute VTE	187.4	75	74.2	0.772	OR=13.375, P=0.001
Köse et al <sup>9</sup>	2020	Turkey	Retrospective	103	67.6±13.1 <sup>a</sup>	PE	39 months	Probability of PE and long-term mortality	NA	NA	NA	NA	OR:1.0, p=0.453; HR:1.0, p=0.545 (Moderate-low and low risk PE); HR:1.01, p=0.046 (Moderate-high and high risk PE)
Liu et al <sup>17</sup>	2020	China	Retrospective	101	64.00 (57.50–71.00) <sup>b</sup>	PAPE	30 days	30-day mortality	NA	NA	NA	NA	NA, p=0.193
Phan et al <sup>20</sup>	2020	USA	Retrospective	191	59.5±16.0 <sup>a</sup> (survived), 62.3 ±15.2 <sup>a</sup> (died)	APE	In hospital	All-cause and In-hospital mortality	256.6	53.6	82.8	0.693	NA, p<0.01
Ghaffari et al <sup>23</sup>	2020	USA	Retrospective	492	62.1±17.2 <sup>a</sup>	APE	12 months	Mortality	12.8	61	63.2	0.61	NA, p<0.01
Kasapoğlu et al <sup>14</sup>	2019	Turkey	Retrospective	550	68 (19–86) <sup>b</sup>	APE	30 days	30-day mortality	170	63	53	0.582	HR=1.4, p=0.503
Telo et al <sup>19</sup>	2019	Turkey	Retrospective	82	61.18 ±15.51 <sup>a</sup>	APE	30 days	In-hospital mortality and 30-day mortality	156	74	64	0.717	OR=6.325, p<0.01

(Continued)

Table 2 (Continued).

Study	Year	Country	Study Design	Number of Individuals	Age (Years)	VTE Type	Follow Up	Outcomes	PLR Cut-Off	Sensitivity (%)	Specificity (%)	AUC	OR/HR and p value
Farah et al <sup>25</sup>	2019	Israel	Retrospective	272	62±18.9 <sup>a</sup>	Acute VTE	NA	Probability of acute VTE	NA	NA	NA	NA	NA, p>0.05
Ertem et al <sup>24</sup>	2018	Turkey	Retrospective	294	67.21 ±14.74 <sup>a</sup>	APE	30 days	In-hospital mortality and 30-day mortality	NA	NA	NA	NA	NA, p=0.241
Grilz et al <sup>33</sup>	2018	Austria	Retrospective	128	62 (50–68) <sup>b</sup>	VTE	24 months	Probability of VTE and 24-month mortality	264	NA	NA	NA	HR=1.5, p<0.001
Fuentes et al <sup>48</sup>	2018	USA	Retrospective	13	58 (51–64) <sup>b</sup>	VTE	21.3 months	Probability of acute VTE	NA	NA	NA	0.4	HR=0.8, p=0.8
Artoni et al <sup>26</sup>	2018	Italy	Retrospective	486	47.9±16.1 <sup>a</sup>	VTE	NA	Probability of acute VTE	NA	NA	NA	NA	OR=0.89, p>0.05
Yao et al <sup>28</sup>	2018	China	Retrospective	120	64.1 ± 13.2 <sup>a</sup>	DVT	In hospital	Probability of acute DVT	NA	NA	NA	0.561	OR=0.99, p<0.001 (postoperative PLR)
Tham et al <sup>49</sup>	2018	USA	Retrospective	306	61.82 ± 14.44 <sup>a</sup>	VTE	30 days	Probability of VTE	320	97.66	71.43	0.905	OR=95.95, p<0.001
Jia et al <sup>18</sup>	2017	China	Retrospective	154	62.54 ± 16.90 <sup>a</sup> (survived), 56.60 ± 14.80 <sup>a</sup> (died)	APE	30 days	30-day mortality	NA	NA	NA	NA	NA, p=0.246

Ming et al <sup>34</sup>	2017	China	Retrospective	115	52.17 ± 14.13 <sup>a</sup>	Acute DVT	NA	Probability of acute DVT	NA	NA	NA	0.61	NA, p>0.05
Ateş et al <sup>8</sup>	2017	Turkey	Retrospective	639	64.1 ± 15.8 <sup>a</sup>	APE	In hospital	Probability of PE	NA	NA	NA	0.877	OR:1.59, p<0.001 (massive APE)
Karataş et al <sup>22</sup>	2016	Turkey	Retrospective	203	65.8 ± 18.1 <sup>a</sup>	APE	20 months	30-day mortality and long-term mortality	NA	NA	NA	NA	HR=1.002, p=0.01
Ma et al <sup>16</sup>	2016	China	Retrospective	248	66 (52–74, survived) <sup>b</sup> , 75 (65–83, died) <sup>b</sup>	APE	30 days	30-day mortality	325	65	80.7	0.789	OR = 1.002, p=0.003
Çelik et al <sup>10</sup>	2015	Turkey	Retrospective	112	59 ± 16 <sup>a</sup>	APE	In hospital	Probability of PE	NA	NA	NA	NA	OR=0.998, p=0.340
Kundi et al <sup>45</sup>	2015	Turkey	Retrospective	646	60 ± 16 <sup>a</sup>	APE	In hospital	In-hospital mortality	149	77.1	76.3	0.860	NA, p<0.001
Ferroni et al <sup>35</sup>	2014	Italy	Retrospective	55	NA	DVT	9 months	Probability of acute DVT	260	30	80	0.54	HR=2.4, p=0.027
Yang et al <sup>47</sup>	2014	China	Retrospective	76	62.0 ± 8.9 <sup>a</sup>	VTE	2 months	Probability of VTE	260	NA	NA	NA	OR=2.757, P=0.025

Notes: <sup>a</sup>Mean±standard deviation; <sup>b</sup>Interquartile range.

Abbreviations: PE, pulmonary embolism; APE, acute pulmonary embolism; PAPE, postoperative acute pulmonary embolism; DVT, deep venous thrombosis; VTE, venous thromboembolism; NA, not available; HR, hazard ratio; OR, odds ratio.

Duman et al also identified there was no significant difference in PLR levels between dead and surviving subgroups in 828 PE patients ( $p=0.13$ ) and that PLR was not an independent risk factor for death ( $p>0.05$ ).<sup>21</sup> Ertem et al found that PLR was also not significantly associated with death in 294 patients with APE ( $p=0.241$ ).<sup>24</sup> Liu et al also revealed that PLR was not an independent predictor of 30-day mortality in patients with PAPE ( $p=0.193$ ).<sup>17</sup>

PLR is a predictor of the occurrence of VTE in cancer patients. Grilz et al identified a statistically significant association between PLR and the occurrence of VTE in 1469 cancer patients, with a HR of 1.5 (95% CI: 1.4–1.7,  $p<0.001$ ).<sup>33</sup> Yamagata et al identified a strong correlation between preoperative PLR and the incidence of postoperative VTE in 101 patients with oral cancer (OR=13.375, 95% CI: 2.950–63.044,  $p=0.001$ ).<sup>46</sup> The predictive sensitivity of PLR was 75.0%, specificity was 74.2%, AUC was 0.772 ( $p=0.002$ ). Yang et al observed that significantly elevated PLR level was an independent predictor of VTE in cancer patients (OR=2.757, 95% CI: 1.655–3.862,  $p=0.025$ ).<sup>47</sup> Ferroni et al showed a higher PLR in symptomatic VTE patients after chemotherapy than before chemotherapy ( $p=0.040$ ) and PLR was an independent risk factor for the onset of VTE (HR=2.4,  $p=0.027$ ).<sup>35</sup> ROC analysis showed a sensitivity of 30% and specificity of 80% for PLR, with an AUC of 0.54.

Some studies have also found that PLR is not significantly associated with the occurrence of VTE. Fuentes et al revealed an association between PLR and mortality in 112 patients with gastric cancer ( $p<0.01$ ), but PLR was not significantly different in patients with and without VTE ( $p=0.751$ ).<sup>48</sup> Artoni et al detected that patients with high PLR did not have an increased risk of VTE in 486 patients (OR=0.89, 95% CI: 0.46–1.76).<sup>26</sup> Farah et al observed a significantly higher PLR in 272 patients with acute VTE ( $p=0.014$ ), but PLR was not an independent predictor ( $p>0.05$ ).<sup>25</sup> Ming et al discovered a significantly higher PLR in 105 patients with acute DVT than in controls ( $p=0.005$ ), while PLR was also not an independent risk factor ( $p>0.05$ ).<sup>34</sup>

PLR also has some predictive value for the onset of VTE in patients after surgical procedures. Yao et al identified a higher preoperative PLR than postoperative PLR in 733 patients after total joint replacement ( $p=0.002$ ).<sup>28</sup> Multiple logistic regression analysis showed that postoperative PLR was independently associated with the occurrence of DVT (OR=0.99, 95% CI: 0.98–0.99,  $p<0.001$ ). ROC analysis showed an AUC of 0.513 (95%

CI: 0.453–0.573) for preoperative PLR and an AUC of 0.561 (95% CI: 0.510–0.611) for postoperative PLR. Tham et al found seven patients (22.9%) with VTE among a total of 306 patients with head and neck cancer who underwent surgery.<sup>49</sup> PLR was strongly associated with the occurrence of VTE with an OR of 95.95, sensitivity of 97.66%, specificity of 71.43% and AUC of 0.905 (95% CI, 0.82–0.98). Nevertheless, among patients with hip fracture, Peng et al found that PLR levels were higher in patients with VTE than in those without VTE, but PLR was not an independent predictor of VTE after hip fracture ( $p=0.051$ ).<sup>31</sup>

Furthermore, Kurtipek et al found significantly higher PLR values in 71 patients with APE compared to healthy controls ( $140.64\pm126.68$  vs  $112.45\pm57.62$ ,  $p=0.003$ ), suggesting that PLR may be associated with pulmonary artery endothelial cell dysfunction.<sup>38</sup> Kuplay et al discovered that PLR was related to thrombus location, with a higher mean PLR in proximal DVT than distal DVT ( $1.77\times10^7\pm1.3\times10^7$  vs  $1.49\times10^7\pm1.08\times10^7$ ;  $p=0.03$ ), but PLR was not increased with the number of venous segments involved ( $p=0.097$ ).<sup>39</sup>

There are relatively few meta-analyses of the clinical value of NLR and PLR in VTE disease. Wang et al conducted a meta-analysis of seven studies and found that NLR and PLR were both significantly associated with mortality in patients with PE.<sup>50</sup> NLR correlated significantly with overall (short-term and long-term) mortality (OR 10.13, 95% CI 6.57–15.64,  $p<0.001$ ) and short-term (in-hospital and 30-day) mortality (OR 8.43, 95% CI 5.23–13.61,  $p<0.001$ ) in patients with PE. PLR was significantly associated with overall mortality (OR 6.32, 95% CI 4.52–8.84,  $p<0.001$ ), short-term mortality (OR 6.69, 95% CI 2.86–15.66,  $p<0.001$ ) and long-term mortality (OR 6.11, 95% CI 3.90–9.55,  $p<0.001$ ).

## Monocyte-Related Indicators and VTE

Lymphocyte/monocyte ratio (LMR), monocyte/lymphocyte ratio (MLR) and monocyte count have been applied in studies concerning the diagnosis and prognosis of mortality in VTE. Köse et al found that LMR was associated with prognosis of mortality in low risk and medium-low risk PE (HR=1.58,  $p=0.046$ ) and not with prognosis of mortality in medium-high and high-risk PE (HR=0.95,  $p=0.751$ ).<sup>9</sup> Ertem et al discovered that LMR was higher among deaths in PE patients ( $p<0.001$ ).<sup>24</sup> LMR was an



independent risk factor for death (HR=0.211,  $p=0.001$ ). ROC analysis showed a cutoff value of 1.96 for LMR, a sensitivity of 77%, a specificity of 79% and an AUC of 0.851 (95% CI: 0.802–0.900,  $p<0.001$ ). However, Liu et al identified that MLR was not an independent predictor of 30-day mortality in patients with PAPE ( $p>0.05$ ).<sup>17</sup> Peng et al also identified that MLR was not an independent predictor of the occurrence of VTE after hip fracture, although MLR was higher than in patients without VTE ( $p=0.062$ ).<sup>31</sup>

The monocyte count also has some predictive value for VTE. Rojnuckarin et al found that monocyte count was significantly higher in 28 patients of solid tumours with VTE compared to 280 patients without VTE ( $p=0.013$ ).<sup>51</sup> Monocyte count over  $0.5 \times 10^9/L$  was significantly associated with VTE and was an independent predictor of VTE (OR=5.0, 95% CI: 1.62–15.5,  $p=0.005$ ). Among 70 VTE patients, Wypasek et al found that VTE was associated with increased non-classical and intermediate monocytes, which were higher in VTE patients than in controls ( $16.8 \pm 9.3$  vs  $10.4 \pm 4.0$  cells/ $\mu L$  and  $64.1 \pm 25.2$  vs  $44.1 \pm 19.2$  cells/ $\mu L$ ,  $p<0.001$ ).<sup>52</sup> Maldonado-Peña et al identified a significantly higher monocyte count in 46 patients with DVT, which was strongly associated with the development of DVT (OR=9.35, 95% CI: 3.2–27.3).<sup>53</sup> ROC analysis showed an AUC of 0.742, a sensitivity of 67.3%, a specificity of 80%, a positive predictive value (PPV) of 79.49% and a negative predictive value (NPV) of 63.9%. Nonetheless, Basavaraj et al identified 429 (17.1%) VTEs in 25,127 patients with a mean follow-up time of 12.5 years.<sup>54</sup> In the first year, the risk of VTE was increased 2.5-fold in patients in the upper tertile of monocyte count ( $\geq 0.7 \times 10^9/L$ ) compared to those in the lower tertile ( $\leq 0.4 \times 10^9/L$ ) (HR:2.51; 95% CI: 0.69, 9.12,  $p=0.07$ ). In the third year, the risk of VTE was increased 1.5-fold (HR:1.58; 95% CI: 0.84, 2.99,  $p=0.07$ ) in patients in the upper tertile of monocyte counts ( $\geq 0.7 \times 10^9/L$ ) compared to those in the lower tertile ( $\leq 0.4 \times 10^9/L$ ). Throughout the study period, the risk estimates decreased progressively and there was no association between monocyte count and VTE at the end of follow-up.

The monocyte count has shown limited clinical value in cancer patients with VTE. Go et al found that VTE occurred in 134 (7.9%) of 1707 patients with lung cancer and that monocyte count was associated with mortality (HR:1.994, 95% CI: 1.137–3.498,  $p=0.016$ ).<sup>55</sup> However, Lopez-Salazar et al identified 16 of 119 (13.4%) patients with ovarian cancer who experienced VTE as having

a significantly higher monocyte count ( $p=0.042$ ), whereas monocyte count was not an independent predictor of VTE and mortality.<sup>56</sup>

The other two reports proposed possible mechanisms for the involvement of monocytes in VTE. Chirinos et al showed significantly higher levels of endothelial micro-particle (EMP)-monocyte conjugates in 25 patients with VTE (3.3 fluorescence intensity units [FLIU], IQR 2.96–3.91) than in controls as well (2.5 FLIU; IQR 2.13–2.83;  $p=0.002$ ).<sup>57</sup> Shih et al revealed significantly higher levels of circulating platelet-monocyte aggregates (PMAs) expression ( $p<0.001$ ) in 32 elderly patients experiencing postoperative VTE, which correlated with CRP levels ( $r^2=0.536$ ,  $p=0.004$ ).<sup>58</sup>

## SII and VTE

SII has been confirmed to be associated with cancer, but recent studies have shown its remarkable clinical value for both the diagnosis and prognosis of mortality in VTE.<sup>59–61</sup> Gok et al identified elevated SII levels in 442 patients with APE and a progressive increase from non-massive to massive APE ( $p<0.001$ ).<sup>62</sup> It was also significantly higher in patients who died in-hospital ( $p<0.001$ ). Multivariate analysis showed that SII was an independent predictor of massive APE (OR:1.005, 95% CI: 1.002–1.007,  $p<0.001$ ), with an optimal cut-off value of 1161, sensitivity of 91%, specificity of 90% and AUC of 0.957 (95% CI: 0.935–0.979). Peng et al discovered an increased SII in patients with VTE compared to those without VTE.<sup>31</sup> And SII was an independent predictor of VTE after hip fracture in elderly patients with an OR of 1.004 (95% CI: 1.001–1.008,  $p=0.001$ ). ROC analysis revealed a cut-off value of 847.78, a sensitivity of 53.8%, a specificity of 92.3%, and an AUC of 0.795 (95% CI: 0.710–0.880,  $p<0.001$ ).

## Eosinophils and VTE

The eosinophil count also has a predictive capability for VTE and may be associated with in-hospital mortality. Among 63 patients with eosinophilia, Liu et al discovered that PE occurred in 31 (50.9%) patients with a peak absolute eosinophil count  $>6.3 \times 10^9/L$  (OR:5.55, 95% CI: 1.292–23.875,  $p=0.021$ ), with a sensitivity of 83.9%, a specificity of 75.0% and an AUC of 0.684.<sup>63</sup> Persistence of eosinophilia over 13.9 months was an independent risk factor for PE with an OR of 4.51 (95% CI: 1.123–18.09,  $p=0.034$ ). Réau et al identified VTE in 29 (53.7%) of 54 patients with eosinophilia, and persistent eosinophilia was closely associated with a shorter time to VT recurrence



(HR 7.48, CI95%:1.94–29.47,  $p=0.015$ ).<sup>64</sup> The eosinophil count was not significantly elevated in patients with solid tumours combined with VTE ( $p=0.138$ ), whereas it was significantly correlated with in-hospital deaths ( $p=0.027$ ), as reported by Rojnuckarin et al.<sup>51</sup> Nevertheless, the opposite conclusion was reached by two studies on eosinophil count. Wypasek et al identified that there was no significant increase in eosinophil count among 70 patients with VTE compared to controls ( $p=0.62$ ).<sup>52</sup> Maldonado-Peña et al also identified there was no apparent rise of eosinophil count in 46 patients with DVT ( $p=0.092$ ).<sup>53</sup>

## Platelet-Related Indicators with VTE

Among 639 patients, Ates et al detected WMR (white blood cell to mean platelet volume ratio) (OR:1.22, AUC:0.762,  $p<0.001$ ); MPR (mean platelet volume to platelet ratio) (OR:0.33, AUC:0.656,  $p<0.001$ ); RPR (red distribution width/platelet ratio) (OR:0.68, AUC:0.719,  $p<0.001$ ) were all of certain diagnostic value for massive APE.<sup>7</sup> Ghaffari et al found that mean platelet volume (MPV) was predictive of in-hospital mortality in 492 APE patients, with a cut-off value of 9.85fl, an AUC of 0.67, predictive sensitivity of 81% and specificity of 49.6%.<sup>23</sup> In-hospital mortality was also highly correlated with platelet distribution width (PDW) with a cut-off value of 13.6%, and AUC of 0.66, predictive sensitivity of 66.7% and specificity of 65.2%. However, Duman et al observed that among 828 PE patients, the Platelet/MPV ratio was not significantly different between the deaths and survivors ( $p=0.73$ ) as well as not being an independent risk factor for death.<sup>21</sup>

Farah et al identified MPV to be significantly elevated in 272 patients with acute VTE ( $p=0.008$ ).<sup>25</sup> A multivariate logistic regression model found that MPV could predict acute VTE (OR:1.5, 95% CI:1.07–2.12,  $p=0.02$ ). ROC analysis showed a cut-off value of 8.6, an AUC of 0.61, a sensitivity of 52% and a specificity of 67%. Chirinos et al found increased activation of platelets ( $p$ -selectin 35.2 vs 5.0 fluorescence intensity units;  $p<0.0001$ ) and leukocytes (CD11b 13.9 vs 7.7 U;  $p=0.004$ ) in 25 patients with VTE.<sup>57</sup> Platelet and leukocyte polymer (PLC) (61.7% vs 39.6%;  $p=0.01$ ) was also significantly increased. CD11b expression in leukocytes was strongly correlated with PLC ( $r=0.74$ ;  $p<0.0001$ ), suggesting that PLC formation regulates leukocyte activation and participates in the link between thrombosis and inflammation. Ming et al, however,

also detected a significantly higher MPV/PDW/MPVLR in 105 patients with acute DVT than in controls ( $p=0.044/0.017/0.001$ ), but neither was an independent risk factor.<sup>34</sup> From the 119 patients with ovarian cancer, Lopez-Salazar et al discovered that 16 (13.4%) patients experienced VTE, 37.8% with a baseline platelet value over  $450 \times 10^9/L$  and 63.8% with a value over  $350 \times 10^9/L$ , although there was no significant correlation between thrombocytosis and the incidence of VTE and mortality.<sup>56</sup>

Few meta-analyses have been conducted on the clinical value of platelet-related indicators in VTE. A meta-analysis by Kovács et al showed that MPV was elevated in patients with DVT than in controls ( $p<0.001$ ), while there was no significant increase in patients with PE.<sup>65</sup> Subgroup analysis showed that PLT was significantly lower in patients with PE than in controls ( $p<0.05$ ). Summary ROC (SROC) analysis showed a diagnostic OR (DOR) of 4.76 (95% CI: 2.3–9.85), diagnostic accuracy of 0.66 and AUC of 0.745 (95% CI: 0.672–0.834) for MPV.

In conclusion, current studies have confirmed the diagnostic and prognostic value of immune/inflammatory biomarkers regarding VTE. NLR appears to provide promising predictive capability for VTE onset and prognosis of mortality, which deserves to be validated in more clinical practice. PLR also has certain diagnostic and prognostic value, but further research is needed to determine its reliability and stability. Monocytes, eosinophils and platelet-related indicators show some clinical association with VTE, although the predictive capabilities are mediocre. SII is of promising potential value for VTE and deserves more investigations.

## Abbreviations

APE, acute pulmonary embolism; AUC, area under the curve; CI, confidence interval; COVID-19, corona virus disease 2019; DVT, deep venous thrombosis; DOR, diagnostic OR; DFS, disease-free survival; GCS, glucocorticoid; HR, hazard ratio; LMR, lymphocyte/monocyte ratio; MLR, monocyte/lymphocyte ratio; MPR, mean platelet volume to platelet ratio; MPV, mean platelet volume; NA, not available; NLR, neutrophil/lymphocyte ratio; OR, odds ratio; OS, overall survival; PE, pulmonary embolism; PAPE, postoperative acute pulmonary embolism; PLR, platelet/lymphocyte ratio; PLC, platelet and leukocyte polymer; PVT/HVTT, portal vein/hepatic vein tumour thrombosis; ROC, receiver operating characteristic curve; SII, systemic immune/inflammatory index; SROC, Summary ROC; VTE, venous thromboembolism; WMR, white blood cell to mean platelet volume ratio.

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