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Lymphocytes, Mean Platelet Volume, and Albumin in Critically Ill COVID-19 Patients with Venous Thromboembolism

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Abstract

As one of the frequent complications leading to poor prognosis in hospitalized COVID-19 patients, a better understanding of venous thromboembolism (VTE) in COVID-19 patients is needed. We conducted a single-center, retrospective study on 96 COVID-19 patients admitted to the intensive care unit (ICU) from April to June 2022, in Shanghai Renji Hospital. Records of these COVID-19 patients upon admission were reviewed for demographic information, co-morbidities, vaccinations, treatment, and laboratory tests. VTE occurred in 11 (11.5%) cases among 96 COVID-19 patients despite the standard thromboprophylaxis since ICU admission. In COVID-VTE patients, a significant increase in B cells and a decrease in Ts cells were observed and a strong negative correlation ($r = -0.9524$, $P = .0003$) was found between these two populations. In COVID-19 patients with VTE, increased MPV and decreased albumin levels were seen in addition to the common VTE indicators of D-dimer abnormalities. The altered lymphocyte composition in COVID-VTE patients is noteworthy. In addition to D-dimer, MPV and albumin levels might be novel indicators for the risk of VTE in COVID-19 patients.

Keywords

venous thromboembolism, COVID-19, lymphocytes, MPV, albumin

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Introduction

Since December 2019, the world has experienced an outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in hundreds of millions of confirmed cases and millions of deaths worldwide. Ever since then, SARS-CoV-2 has evolved with a series of mutations. In late February 2022, SARS-CoV-2 Omicron BA.2.2 sub-lineage swept through Shanghai.[1] Although Omicron BA.2 evolves toward less virulent, a considerable number of cases in the unvaccinated elderly population still present severe or critical manifestations.[1]

Of note, venous thromboembolism (VTE) is a frequent complication in hospitalized COVID-19 patients and associated

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with poor outcomes.[2] VTE, which mainly involves pulmonary embolism (PE) and deep vein thrombosis (DVT) is one of the major concerns in different clinical scenarios, especially in intensive care units (ICU). Identifying COVID-19 patients at increased risk for VTE can help in developing a VTE screening program. However, the incidence of VTE in COVID-19 patients remains undetermined, and the specific evaluation of the VTE risks in COVID-19 patients has yet to be answered.

Cancer, prior VTE, major general surgery, multiple trauma, and systemic inflammation are believed to increase the risk of VTE.[3,4] Infection of SARS-CoV-2 is often accompanied by a hyperinflammatory response and systemic coagulation dysfunction that would remarkably increase the risk of VTE.[2] Inflammation is involved in both COVID-19 and VTE, which makes it conceivable that the inflammation-related factors such as C-reactive protein (CRP), lymphocytes, mean platelet volume (MPV), serum albumin level, and IL-6 are indicative of VTE risk in COVID-19 patients.[5-8]

The objectives of this study were to demonstrate the incidence of VTE in critically ill COVID-19 patients and evaluate the potential risk factors and indicators for VTE in COVID-19 patients admitted in ICU.

Methods and Materials

This is a single-center, retrospective study. The data were extracted from the medical records of 96 COVID-19 patients admitted to the ICU from April 7, 2022, to June 18, 2022, in Shanghai Renji Hospital South Campus Affiliated to Shanghai Jiaotong University. The diagnosis of COVID-19 was confirmed by real-time polymerase chain reaction (RT-PCR). We reviewed the laboratory tests upon the time of admission.

All patients were treated with enoxaparin 40 mg once a day or twice a day for thromboprophylaxis. Venous duplex-ultrasound (venue, GE) was performed on all ICU patients for DVT screening on days 3 and 10 after admission to ICU, and when DVT was highly suspected (increased D-dimer or lower limbs swelling), venous duplex-ultrasound would be performed immediately. If PE was suspected, a CT pulmonary angiogram (CTPA) would be performed to confirm diagnosis.

Classification of COVID-19

COVID-19 patients were classified into the following illness severity categories:

Asymptomatic—without symptoms that are consistent with COVID-19.

Mild—various symptoms of COVID-19 (eg, fever, cough, malaise, headache, muscle pain, nausea, and diarrhea); no shortness of breath, dyspnea, or abnormal chest imaging.

Moderate—with fever, respiratory, or other symptoms; imaging finding of pneumonia.

Severe—a respiratory rate $\geq$30 breaths/min; $SpO_2 \leq 93\%$ at rest; a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) $\leq$ 300 mm Hg; progressive clinical symptoms with lung imaging showing >50% progression of the lesion within 24–48 h.

Critical—respiratory failure, needs mechanical ventilation; septic shock; and/or multiple organ dysfunction.

Statistical Analysis

The data are given as mean $\pm$ standard deviation (SD) of the indicated number of the subjects. Categorical variables were analyzed by χ^2 test. For the comparison of the absolute counts and frequencies of the blood cells and other laboratory tests, normal distribution of values was assessed using the Kolmogorov–Smirnov test. The Mann–Whitney test was performed on the unpaired data that did not pass the Kolmogorov–Smirnov test. For normal distributed paired data, an unpaired t-test was performed. When the data passed the Kolmogorov–Smirnov test, Spearman test was used for calculating correlations, while for the data that did not pass the Kolmogorov-Smirnov test, non-parametric Spearman test was used.

Results

Baseline Characteristics

A total of 96 COVID-19 patients admitted to the ICU were included in this study. The demographic and laboratory characteristics of all patients are shown in Table 1. The mean age of all patients was 73 years old (range 24–98), and 45.5% (44 patients) of them were female. Among 96 patients, 11 (11.5%) developed VTE. Except for the VTE history ($P = .0023$), there were no significant differences in baseline characteristics.

Association Between Lymphocytes and VTE in COVID-19 Patients

Lymphocyte response plays an essential role in viral infection, and the changes in lymphocytes composition were investigated. Figure 1 shows the changes of the lymphocyte subsets. Although there was no significant difference in the absolute number of lymphocytes between COVID-19 patients with and without VTE (Figure 1A), some changes were observed in the subsets. Compared with control group, the percentage and absolute count of B cells were remarkably increased in COVID-VTE patients upon admission (Figure 1I and J). Moreover, we observed increased B cell frequency ($\geq$19.3%) is significantly associated with increased VTE incidence in COVID-19 patients instead of COVID-19 severity (Supplemental Table S1). With correlation analysis, the changes of B cells in COVID-VTE patients are strongly negatively correlated with the change of Ts cells other than the levels of MPV, CRP, and albumin (Figure 2B and C).

The percentages and absolute counts of the T cell and suppressor (Ts) cells decreased in COVID-VTE patients (Figure 1B, C, E, and F), with the frequency change in Ts cells being significant (Figure 1E). Previous study reported

Table 1. Baseline Characteristics of the Patients.

	All patients ($n = 96$)	COVID ($n = 85$)	COVID-VTE ($n = 11$)	*P*-value
Characteristic				
Mean age (yr)	72.8	72.5	75.9	.63
Range (yr)	24–98	24–98	52–90	
≥65: no. (%)	69 (71.9)	61 (71.8)	8 (72.7)	.96
<65: no. (%)	27 (28.1)	24 (28.2)	3 (27.3)	.96
Male: no. (%)	53 (55.2)	48 (56.5)	5 (45.5)	.49
Female: no. (%)	43 (44.8)	37 (43.5)	6 (54.5)	.49
COVID-19 severity: no. (%)				.60
Moderate illness	15 (15.6)	14 (16.5)	1 (9.1)	
Severe illness	57 (59.4)	51 (60.0)	6 (54.5)	
Critical illness	24 (25.0)	20 (23.5)	4 (36.4)	
Comorbidity: no. (%)				
Hypertension	42 (43.8)	38 (44.7)	4 (36.4)	.60
Coronary artery disease	18 (18.8)	16 (22.4)	2 (18.2)	.82
Diabetes	16 (16.7)	13 (15.3)	3 (27.3)	.32
CKD	8 (8.3)	6 (7.1)	2 (18.2)	.21
Ischemic stroke	27 (28.1)	23 (27.1)	4 (36.4)	.52
Hepatic disease[a]	6 (6.25)	5 (5.9)	1 (9.1)	.68
Cancer	18 (18.8)	15 (17.6)	3 (27.3)	.44
VTE history: no. (%)	2 (2.1)	1 (1.2)	2 (18.2)	**<.01**
SARS-CoV-2 vaccination[b]: no. (%)	18 (18.8)	18 (21.2)	0 (0)	.41
1 dose	4 (4.2)	4 (4.7)	0 (0)	
2 doses	9 (9.4)	9 (10.6)	0 (0)	
3 doses	5 (5.2)	5 (5.9)	0 (0)	
Anti-platelet therapy[c]: no. (%)	14 (14.6)	12 (14.1)	2 (18.2)	.63
Paxlovid treatment: no. (%)	65 (67.7)	58 (68.2)	7 (63.6)	.76

[a]Including hepatitis B/C infection, autoimmune hepatitis, hepatic abscess, cirrhosis.
[b]Inactivated SARS-CoV-2 vaccine: BBIBP-CorV or Corona Vac.
[c]Aspirin was applied as anti-platelet therapy in investigated patients.

the prominently decreased CD8 T cells resulting in increased CD4:CD8 ratio in COVID-19 patients.[9] In our study, a significantly increased CD4:CD8 ratio was found in COVID-VTE patients (Figure 1D). Moreover, the negative correlation between CD4:CD8 ratio and T cell count in COVID-VTE patients is of note (Figure 2A red, $r = -0.6240$, $P = .0402$), while no significant correlation was observed in control group (Figure 2A black, $r = -0.1139$, $P = .2991$).

Other leukocyte subsets, such as neutrophils, monocytes, and NK cells, were investigated and there were no significant differences between the groups though some trends were present (Figure 1).

Enlarged Platelets and Lower Albumin Level Indicates the Higher Risk of VTE

There are many other factors involved in assessing VTE risk. For the platelet analysis, platelet count and mean platelet volume (MPV) were evaluated. Absolute platelet count did not change in both group (Figure 1N). The mean of the MPV remained in the normal range in both groups, while the MPV of COVID-VTE patients significantly increased compared with control group (Figure 1O). Elevated D-dimer and CRP levels are associated with adverse outcomes in COVID-19 patients,[10] and the remarkable increase of D-Dimer and CRP were observed in COVID-VTE patients (Figure 2P and Q). Low serum albumin was proposed to be a moderate risk marker of VTE,[11] and in our study lower albumin level was observed in COVID-VTE patients (Figure 1R).

Preliminary evidence support that many other indicators, such as elevated IL-6 level (Figure 1S), neutrophil:lymphocyte ratio, platelet:lymphocyte ratio, Th:Ts ratio and low level of lymphocyte:monocyte ratio, are able to assess the risk of VTE in different clinical settings,[12-16] while no significant changes were observed in the present study (Supplemental Figure S1).

Discussion

In this retrospective study of the 96 COVID-19 patients admitted in ICU, we found: (1) the incidence of the VTE in the recruited subjects was 11.5%, and VTE history is more frequent in COVID-VTE patients; (2) The composition of lymphocytes was altered in COVID-VTE patients; and (3) enlarged platelet size and decreased albumin level were observed in COVID-VTE patients.

The incidence of VTE in hospitalized COVID-19 patients varies from 7.9% to 54%,[2,17-19] and among COVID-19 patients admitted to ICU, it is 27.9% according to a meta-analyses.[18]

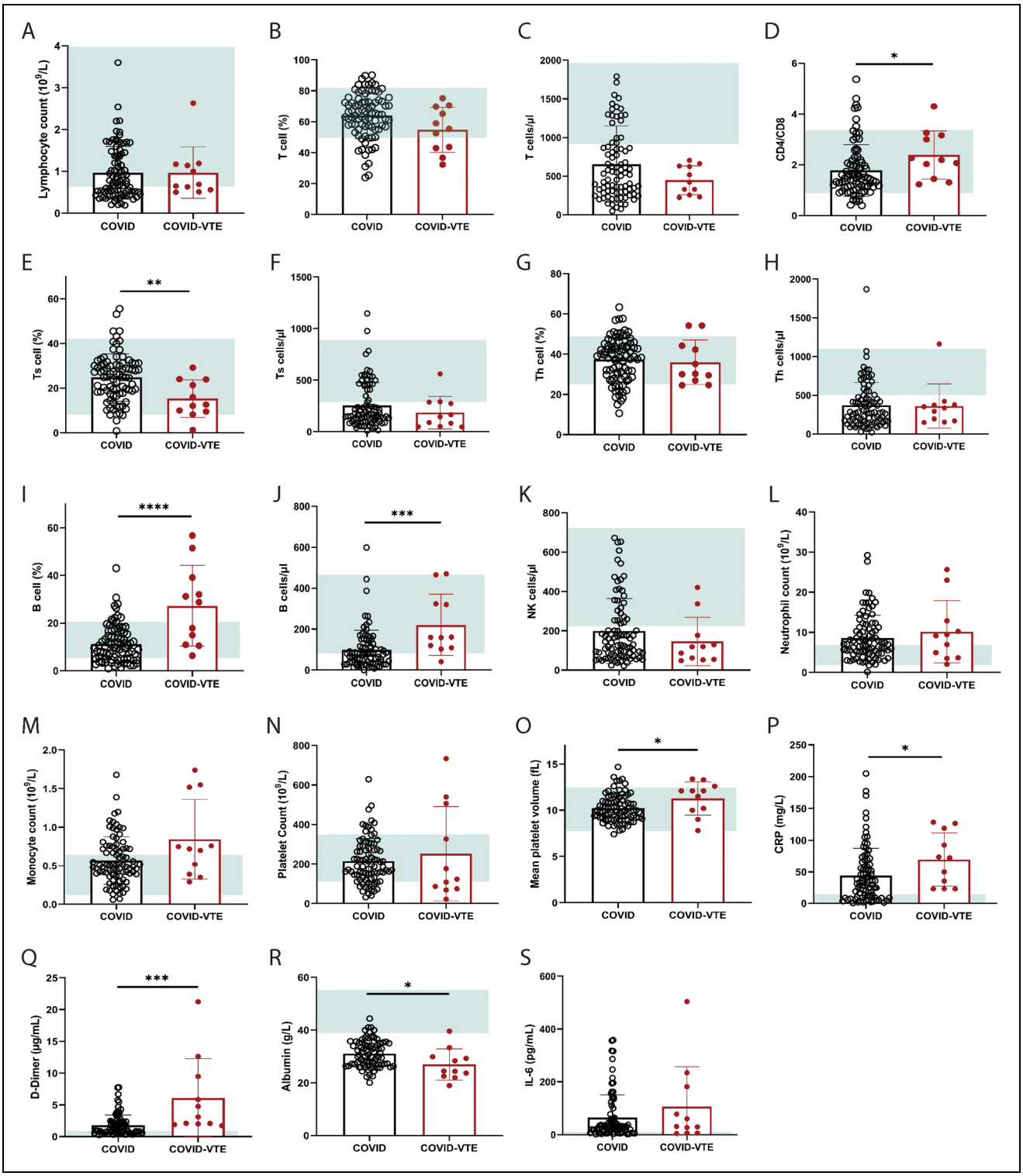

Figure 1. The absolute counts and frequencies of the lymphocytes and its major subsets upon admission. (A–S) The scatter plots with bar graphs display the results of laboratory tests. The clinical normal (healthy) range of each parameter is indicated in green. Each dot represents a COVID-19 patient. Data are shown as mean ± SD. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$, $^{****}P < .0001$.

Although patients could be effectively protected from VTE by the application of thromboprophylaxis, there are evidence showing that patients in ICU receiving thromboprophylaxis still have incidence of VTE ranging from 5% to 37.2%.[20,21] In our study, the relatively low incidence (11.5%) of VTE in ICU COVID-19 patients may be due to the fact that the different

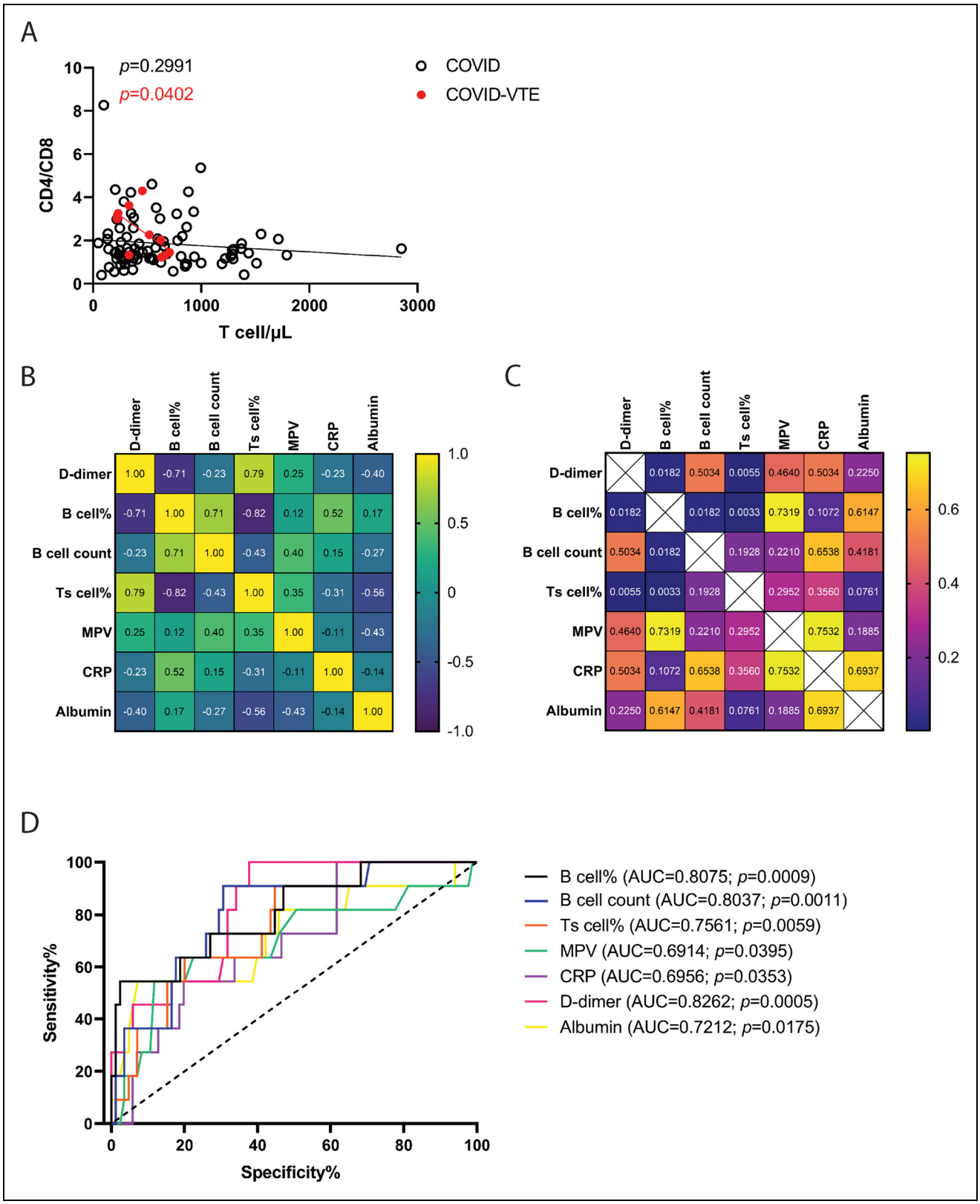

Figure 2. Correlation analysis between CD4:CD8 ratio and T cell count, correlation matrix, and ROC curves of the significantly changed parameters in COVID-VTE patients. (A) The correlation of CD4:CD8 ratio and lymphocyte absolute count in COVID-19 patients without (black) and with (red) VTE. (B and C) Values in cells are Spearman correlation coefficients (B) and correlation *P* values (C). (D) ROC curves of significantly changed parameters in COVID-VTE patients.

VTE routine screening protocol was applied. However, the accurate incidence of VTE in hospitalized COVID-19 patients is still elusive. It cannot be concluded that SARS-CoV-2 infection increases the risk of VTE in ICU patients and more studies are needed.

Notably, even though ICU patients would benefit from thromboprophylaxis with low molecular weight heparin, heparin-induced thrombocytopenia (HIT) remains a non-negligible problem. In the present study, greatly reduced platelet counts were observed in some COVID-VTE cases, whereas heparin-PF4 antibody testing and other laboratory testing for HIT were absent in these patients, making it impossible to exclude HIT in these VTE cases. Meanwhile, vaccine-induced immune thrombotic thrombocytopenia (VITT), which resembles the clinical features of HIT, has been reported mainly in people receiving adenoviral vector vaccines (ChAdOx1 nCov-19, Ad26.COV2.S), and with hundreds of millions of vaccinations, VITT has become a hot topic despite the low incidence.[22] VITT was excluded in COVID-VTE patients since all of them were unvaccinated.

The T cell and B cell responses to SARS-CoV2 infection are critical, but little is known about them. Regarding B cells, virus infection could induce massive plasmablast response, and the strikingly increased frequencies of plasmablasts in circulating B cells were reported during the acute phase of Ebola or Dengue infection.[23,24] In patients with SARS-CoV-2 infection, robust plasmablast response was found in some cases.[9] However, the immune response to SARS-CoV-2 infection is heterogeneous and varies across the trajectory,[9,25] resulting in the inconsistency between studies. Sosa-Hernández and colleagues suggested that COVID-19 patients with severe symptoms had significantly increased B-cell frequencies compared to those with mild/moderate symptoms,[26] while another retrospective study indicated that the decreased B cells could predict the death of COVID-19.[27] In our study, a relatively low B cell count was found in COVID-19 control group (compared with normal range), and significantly increased B cell frequency and absolute count were observed in COVID-VTE patients compared with control group. Furthermore, B-cell frequency above the upper limit (19.3%) appears to be associated with increased VTE frequency, further suggesting that changes in B-cells should be considered more seriously in COVID-19 patients with a higher risk of VTE. In fact, only the whole B cells were investigated in the present study, which cannot reflect the changes of the B cell subsets with greater details. Nevertheless, the role of B cell response in the context of COVID-19 infection with VTE is still debated.

In the previous study, lymphopenia and decreased lymphocyte subsets counts were observed in COVID-19 patients.[27] We noted that the frequencies of T cells in both groups fell into the normal range, while the frequency of T cells in COVID-VTE were lower than control group (not significant). Concerning T cell subsets, frequencies of Ts cells were significantly decreased beyond the lower limit of normal range in COVID-VTE patients, which was reported to be an independent predictor for the poor outcomes of COVID-19.[27] Increased Th/Ts ratio was as well suggested to predict the death in COVID-19 patients,[27] while in our study, Th/Ts ratio in COVID-VTE patients has no significant difference compared with COVID-19 patients without VTE (Supplemental Figure S1). Intriguingly, the change of B cells in COVID-VTE patients are strongly negatively correlated with the change of Ts cells other than the levels of MPV, CRP, and albumin (Figure 2B and C). This might suggest the dysregulated T cell and B cell homeostasis and B cell response in COVID-VTE patients is not simply parallel to the systemic inflammation.[9]

VTE and VTE with severe infection may cause the decreases of CD3+ and CD8+ T lymphocytes and the increase of CD4+ T lymphocytes.[28] While no significant changes were observed on T cell frequency and absolute count (Figure 1B and C), CD4:CD8 ratio was found to be strongly negatively correlated to absolute T cell count (Figure 2A), meaning that the decrease of CD8 + T cells may contribute more to the reduced T cells. Based on the response of T and B cells to the infection of SARS-CoV-2, the "immunotypes" related to the poor outcomes of COVID-19 was proposed in one study,[9] and similarly, the "immunotypes" in COVID-19 patients may provide the insights for the prevention and screening of VTE. The debate on lymphocytes in COVID-19 patients suggests the diversity of the immune response to SARS-CoV-2 infection and adds to its intricacies along with the complications of VTE. Further studies are warranted.

Several studies showed the fall of the platelet count is associated with severe COVID-19 and increased thrombosis events.[29] The significant decreased platelet counts were not observed in the present study, whereas MPV was remarkably increased in COVID-19 patients with VTE. The finding regarding MPV is consistent with the studies indicating that MPV is a risk factor for VTE,[30] as well as a predictor of COVID-19 severity.[31] MPV is inversely correlated with platelet count under physiological conditions in order to maintain hemostasis and keep the platelet mass constant. This suggests that decreased platelet count would be associated with increased MPV. Moreover, increased MPV alone could also reflect increased platelet reactivity, which is important in the pathogenesis of VTE.[32]

Notably, there is accumulating evidence suggesting that low albumin levels are an important predictor of increased risk of VTE due to the inhibition of albumin synthesis in high inflammatory and hypercoagulable states.[11] In line with prior studies demonstrating that lower albumin level is predictive for poor prognosis of COVID-19 patients,[33] we also observed decreased albumin level in COVID-19 patients with VTE, suggesting that albumin may be another biomarker of VTE risk in COVID-19 patients.

The commonly indicated systemic inflammation marker—CRP—had been reported as an important assessment or risk factor for VTE in COVID-19 patients,[10,17,19] and elevated CRP level was found in our COVID-VTE patients. Care should be taken on interpretation of CRP, since CRP is in fact an indicator of inflammation. Although systemic inflammation is associated with increased VTE, CRP, rather than D-dimer, is more influenced by pre-existing disease, and is a distinct marker of inflammation level rather than an indicator of VTE.[3,34]

VTE in COVID-19 patients is the consequence of systemic change involving immune response, platelet activation, and coagulation. Thus, the risk of the VTE in COVID-19 patients cannot be evaluated or predicted by a single factor, the comprehensive factors should be taken into consideration.

Limitation

We do realize that our study has several evident limitations. One of them is the limited sample size, especially the numerally small number of the COVID-VTE patients, resulting in the reduced statistic power. Although retrospective study is a sound tool that can provide an association between the variable and the outcome, the interpretation of the results should be carefully taken before applying them to clinic. As a single-center retrospective study, we are constrained to use existing test results which were not designed for research originally, and the results need to be confirmed in a perspective study.

Conclusions

In conclusion, retrospective study of the records of COVID-19 patients in the ICU led us to conclude that more light should be shed on the changes in lymphocyte subpopulations when considering VTE in patients with COVID-19 admitted to the ICU. Meanwhile, elevated MPV and reduced albumin might be novel reliable assessments for the increased VTE risk in COVID-19 patients. These observations warrant further investigation.

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

References

1. Zhang X, Zhang W, Chen S. Shanghai's life-saving efforts against the current omicron wave of the COVID-19 pandemic. *Lancet*. 2022;399(10340):2011-2012. https://doi.org/10.1016/S0140-6736(22)00838-8
2. Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. *Thromb Res*. 2020;196:67-74. doi: 10.1016/j.thromres.2020.08.020
3. Darzi AJ, Karam SG, Charide R, et al. Prognostic factors for VTE and bleeding in hospitalized medical patients: a systematic review and meta-analysis. *Blood*. 2020;135(20):1788-1810. doi: 10.1182/blood.2019003603
4. Pastori D, Cormaci VM, Marucci S, et al. A comprehensive review of risk factors for venous thromboembolism: from epidemiology to pathophysiology. *Int J Mol Sci*. 2023;24(4):3169. doi: 10.3390/ijms24043169
5. Karagoz I, Aktas G, Yoldas H, et al. Association between hemogram parameters and survival of critically ill patients (1525-1489 Electronic).
6. Branchford BR, Carpenter SL. The role of inflammation in venous thromboembolism (2296-2360 Print).
7. Sit M, Kargi E, Aktas G, Dikbas O, Alcelik A, Savli H. Mean platelet volume should be a useful indicator in diagnosis of Hashimoto's thyroiditis. *Acta Med Mediterr* 2014;30(2):1263-1266.
8. Atak Tel BM, Bilgin S, Kurtkulagi O, et al. Frailty in diabetic subjects during COVID-19 and its association with HbA1c, mean platelet volume and monocyte/lymphocyte ratio. *Clin Diabetol*. 2022;11(2):119-126. doi: 10.5603/dk.a2022.0015
9. Mathew D, Giles JR, Baxter AE, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science*. 2020;369(6508):eabc8511. doi:10.1126/science.abc8511
10. Smilowitz NR, Kunichoff D, Garshick M, et al. C-reactive protein and clinical outcomes in patients with COVID-19. *Eur Heart J*. 2021;42(23):2270-2279. doi: 10.1093/eurheartj/ehaa1103
11. Lutsey PL, Heckbert SR, Cushman M, Folsom AR. Serum albumin and risk of venous thromboembolism. *Thromb Haemost*. 2010;104(07):100-104. doi: 10.1160/th09-12-0856
12. Matsuo K, Hasegawa K, Yoshino K, et al. Venous thromboembolism, interleukin-6 and survival outcomes in patients with advanced ovarian clear cell carcinoma. *Eur J Cancer*. 2015;51(14):1978-1988. doi: 10.1016/j.ejca.2015.07.012
13. Ferroni P, Riondino S, Formica V, et al. Venous thromboembolism risk prediction in ambulatory cancer patients: clinical significance of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio. *Int J Cancer*. 2015;136(5):1234-1240. doi: 10.1002/ijc.29076
14. Yang W, Liu Y. Platelet-lymphocyte ratio is a predictor of venous thromboembolism in cancer patients. *Thromb Res*. 2015;136(2):212-215. https://doi.org/10.1016/j.thromres.2014.11.025
15. Zhu X, Yao Y, Yao C, Zhang P. Predictive value of lymphocyte to monocyte ratio and monocyte to high-density lipoprotein ratio for acute deep vein thrombosis after total joint arthroplasty: a retrospective study. *J Orthop Surg Res*. 2018;13:211-217. doi: 10.1186/s13018-018-0910-2
16. Melazzini F, Colaneri M, Fumoso F, et al. Venous thromboembolism and COVID-19: a single center experience from an academic tertiary referral hospital of Northern Italy. *Intern Emerg Med*. 2021;16(5):1141-1152. doi: 10.1007/s11739-020-02550-6

17. Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis*. 2020;50(1):211-216. doi: 10.1007/s11239-020-02146-z
18. Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019. *Chest*. 2021;159(3):1182-1196. doi: 10.1016/j.chest.2020.11.005
19. Kollias A, Kyriakoulis KG, Stergiou GS, Syrigos K. Heterogeneity in reporting venous thromboembolic phenotypes in COVID-19: methodological issues and clinical implications. *Br J Haematol*. 2020;190(4):529-532. doi: 10.1111/bjh.16993
20. Boddi M, Peris A. Deep vein thrombosis in intensive care. *Adv Exp Med Biol*. 2017;906:167-181. doi:10.1007/5584_2016_114. PMID: 27628009.
21. Zhang C, Zhang Z, Mi J, et al. The cumulative venous thromboembolism incidence and risk factors in intensive care patients receiving the guideline-recommended thromboprophylaxis. (1536-5964 Electronic).
22. Schultz NH, Sorvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. 2021;384(22):2124-2130. doi: 10.1056/NEJMoa2104882
23. McElroy AK, Akondy RS, Davis CW, et al. Human Ebola virus infection results in substantial immune activation. *Proc Natl Acad Sci U S A*. 2015;112(15):4719-4724. doi: 10.1073/pnas.1502619112
24. Wrammert J, Onlamoon N, Akondy RS, et al. Rapid and massive virus-specific plasmablast responses during acute dengue virus infection in humans. *J Virol*. 2012;86(6):2911-2918. doi: 10.1128/jvi.06075-11
25. Wen W, Su W, Tang H, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discov*. 2020;6(1):31. doi: 10.1038/s41421-020-0168-9
26. Sosa-Hernandez VA, Torres-Ruiz J, Cervantes-Diaz R, et al. B cell subsets as severity-associated signatures in COVID-19 patients. *Front Immunol*. 2020;11:611004. doi: 10.3389/fimmu.2020.611004
27. Jiang N, Li Z, Yang B, et al. Peripheral inflammatory cytokines and lymphocyte subset features of deceased COVID-19 patients. *Biomed Res Int*. 2021;2021:9101082. doi: 10.1155/2021/9101082
28. Zhou L, Mao Y, Wang L, et al. Comparison of peripheral blood T lymphocyte immune function among venous thromboembolism patients with and without infection and patients with simple infection (1940-5901 Print).
29. Bao C, Tao X, Cui W, et al. SARS-CoV-2 induced thrombocytopenia as an important biomarker significantly correlated with abnormal coagulation function, increased intravascular blood clot risk and mortality in COVID-19 patients. *Exp Hematol Oncol*. 2020;9(1):16. doi: 10.1186/s40164-020-00172-4
30. Edvardsen MS, Hansen ES, Hindberg K, et al. Combined effects of plasma von Willebrand factor and platelet measures on the risk of incident venous thromboembolism. *Blood*. 2021;138(22):2269-2277. doi: 10.1182/blood.2021011494
31. Quispe-Pari JF, Gonzales-Zamora JA, Munive-Dionisio J, et al. Mean platelet volume as a predictor of COVID-19 severity: a prospective cohort study in the Highlands of Peru. *Diseases*. 2022;10(2):22. doi: 10.3390/diseases10020022
32. Braekkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Størmer J, Hansen JB. Mean platelet volume is a risk factor for venous thromboembolism: the Tromsø study. *J Thromb Haemostasis*. 2010;8(1):157-162. doi: 10.1111/j.1538-7836.2009.03498.x
33. Kheir M, Saleem F, Wang C, Mann A, Chua J. Higher albumin levels on admission predict better prognosis in patients with confirmed COVID-19. *PLoS One*. 2021;16(3):e0248358. doi: 10.1371/journal.pone.0248358
34. Folsom AR, Lutsey PL, Heckbert SR, et al. Longitudinal increases in blood biomarkers of inflammation or cardiovascular disease and the incidence of venous thromboembolism. *J Thromb Haemostasis*. 2018;16(10):1964-1972. doi: 10.1111/jth.14241