Mean Platelet Volume Predicts Severe COVID-19 Illness

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The parameter mean platelet volume (MPV) is a simple and relatively inexpensive laboratory measure that reliably reflects platelet size. Evidence has been provided that increased MPV values may be a hallmark of several thrombotic disorders, including acute coronary syndrome, stroke, venous thromboembolism, abdominal vein thrombosis, and even preeclampsia.[1] Although the clinical significance of this laboratory parameter remains only partially unraveled, an enhanced MPV value mirrors the presence of large (mostly reticulated) platelets in the circulation, which are essentially hyperactivated and hyperreactive elements, thus justifying their frequent association with vascular thrombosis.[2]

Since coronavirus disease 2019 (COVID-19), a life-threatening infectious disease sustained by the severe respiratory syndrome coronavirus 2 (SARS-CoV-2), is frequently complicated by thrombotic episodes, both venous and arterial,[3,4] we provide here an updated analysis of current scientific literature data exploring the association between MPV and illness severity in patients with COVID-19.

We conducted an electronic search in Scopus, MEDLINE (with PubMed interface), and the Web of Science, using the keywords "mean platelet volume" *or* "MPV" *and* "coronavirus disease 2019" *or* "COVID-19" in all fields, with no language or date restriction (i.e., up to February 18, 2021). Two authors analyzed the title, abstract and the full text of all items that could be identified according to the search criteria. Studies reporting MPV values in COVID-19 patients with or without severe illness were included in the pooled analysis. The full list of references of each article was also analyzed, with the purpose of identifying other eligible documents. The mean and standard deviation (SD) of MPV values were then included in a pooled analysis, with calculation of weighted mean difference (WMD) and 95% confidence interval (95% CI) of this parameter in patients with SARS-CoV-2 infection with or without severe disease. When mean value and SD were unavailable, these were extrapolated from available figures or calculated from sample size, median, and interquartile range, as proposed by Hozo et al.[5] When multiple MPV measurements were presented, only values corresponding to peak severity were retained. A quality effects model was originally used, followed by a random effects model with the purpose of adjusting any heterogeneity that emerged among the various studies. The heterogeneity was assessed using χ^2 test and I^2 statistic. The statistical analysis was performed with MetaXL, software version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). The study was conducted in agreement with the declaration of Helsinki and within the terms of local legislation.

The original digital search enabled the identification of a total number of 83 documents. Following the elimination of duplicates across the three scientific databases, 65 were excluded as they did not specifically deal with COVID-19 ($n = 16$), did not include MPV data ($n = 13$), or MPV values stratified for COVID-19 severity could not be retrieved or extrapolated ($n = 17$), were animal studies ($n = 2$), were review articles ($n = 14$) or editorial material ($n = 2$), or presented overlapping information already included in previous investigations ($n = 1$). No interreviewer disagreement emerged. A total number of 18 studies were finally included in our analysis, with 3,433 COVID-19 patients, 780 (22.7%) with severe illness (►**Table 1**).[6–23] All except two were cross-sectional studies, with the majority from China (7; 39%), and used heterogeneous combination of clinical endpoints for defining severity of COVID-19 (44% included respiratory

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Table 1 Summary of clinical studies which have investigated MPV values in COVID-19 patients with or without severe illness

Authors	Setting	Study design	Sample size	Endpoint
Asan et al[6]	Turkey	Cross-sectional	695 (4% severe)	ICU admission
Barrett et al[7]	US	Cross-sectional	100 (32% severe)	Thrombosis or death
Comer et al[8]	Ireland	Cross-sectional	54 (63% severe)	ICU admission
Ding et al[9]	China	Cross-sectional	72 (21% severe)	Respiratory failure and/or ICU admission
Fois et al[10]	Italy	Cross-sectional	119 (24% severe)	Death
Giusti et al[11]	Italy	Cross-sectional	209 (15% severe)	Death
Güçlü et al[12]	Turkey	Cross-sectional	212 (62% severe)	Respiratory failure
Ko et al[13]	Korea	Cross-sectional	333 (43% severe)	ICU admission
Lanini et al[14]	Italy	Longitudinal	379 (11% severe)	Death
Lin et al[15]	China	Cross-sectional	68 (68% severe)	Respiratory failure and/or ICU admission
Mertoglu et al[16]	Turkey	Cross-sectional	555 (4% severe)	ICU admission
Ouyang et al[17]	China	Longitudinal	107 (23% severe)	Death
Taha et al[18]	US	Cross-sectional	81 (81% severe)	Acute kidney injury
Taj et al[19]	Pakistan	Cross-sectional	29 (28% severe)	Respiratory failure
Wang et al[20]	China	Cross-sectional	61 (39% severe)	Respiratory failure and/or ICU admission
Xing et al[21]	China	Cross-sectional	61 (13% severe)	Respiratory failure and/or ICU admission and/or death
Xiong et al[22]	China	Cross-sectional	57 (67% severe)	Respiratory failure and/or ICU admission
Zhang et al[23]	China	Cross-sectional	241 (24% severe)	Respiratory failure and/or ICU admission

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; MPV, mean platelet volume.

failure and/or intensive care unit admission, 33% death, and 6% acute kidney failure or thrombosis; ►**Table 1**).

The results of the pooled analysis of the 18 studies are shown in ►**Fig. 1**. In all studies, the difference of MPV values between patients with or without severe COVID-19 illness was positive, reaching statistical significance in 14 of 18 (78%). Overall, the WMD of MPV was 0.63 (95% CI, 0.35–0.90) fL using a quality effects model (heterogeneity was high, $I^2 = 91\%$), increasing to 0.74 (95% CI, 0.51–0.97) fL using a random effects model. MPV values were found to be increased by 6.3% (95% CI, 3.6–9.0%) in COVID-19 patients with adverse clinical outcomes compared with those without progression to severe disease. In a subanalysis of the four studies that included only mortality as clinical endpoint, the WMD of MPV values in random effects model further increased to 1.2 (95% CI, 0.38–2.01) fL between patients who died and those who survived ($I^2 = 97\%$).[10,11,14,17]

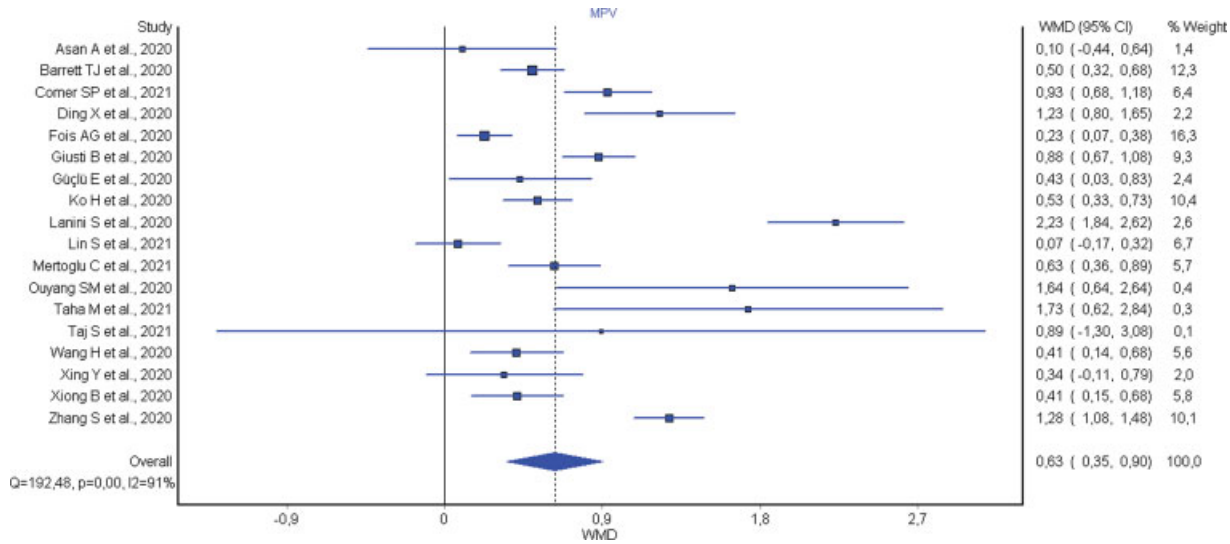

Fig. 1 Weighted mean difference (WMD) and 95% confidence interval (95% CI) of mean platelet volume (MPV) in patients with coronavirus disease 2019 (COVID-19) with or without severe illness.

The results of this pooled analysis of available scientific literature clearly attest that MPV, which reflects larger circulating platelets, may be a significant predictor of adverse clinical progression in patients with COVID-19, playing an even more important role in predicting mortality. This evidence is not unexpected, as platelet biology appears to be largely perturbed in patients with SARS-CoV-2 infection, and further contributes to magnify their risk of developing pulmonary or disseminated thrombosis.[24,25] Although a thoughtful discussion on the interplay between platelets and SARS-CoV-2 infection has already been provided in some previous articles,[24,25] a brief overview on the significance of these findings is perhaps advisable. SARS-CoV-2 can contribute to platelets activation via a variety of mechanisms and different pathways, such as direct binding to platelet surface, provoking endothelial injury, sustaining an inflammation-related release of von Willebrand factor (VWF) compounded by a concomitant decrease in the activity of ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) which would then lead to impaired cleavage of ultralarge VWF, as well as by reducing heparan sulfates at blood vessel surface and impairing generation of vasoeffective mediators (e.g., nitric oxide, prostacyclin, and prostaglandin).[4] Platelet activation may also occur as a consequence of thrombin generation occurring after concomitant activation of blood coagulation.[26] Moreover, direct SARS-CoV-2 and spike protein binding to platelet angiotensin-converting enzyme 2 (ACE2) has been shown to activate platelets in vitro, while spike has been shown to potentiate thrombus formation in vivo. Such SARS-CoV-2/spike to platelet ACE2 binding results in platelet stimulation, causing release of coagulation factors and inflammatory cytokines, with promotion of leukocyte–platelet aggregates formation.[23] All the aforementioned mechanisms may hence synergistically act (or contribute) to generate hyperactive platelets, phenotypically recognizable by an increased size, which would then play a role to trigger the micro- and macrothrombotic events that are commonly seen in COVID-19 patients with severe or critical disease, ultimately fostering unfavorable prognosis, including an enhanced risk of death.[27] Indirect support to this theory emerges from recent evidence that in-hospital aspirin (81 mg daily) administration in COVID-19 patients has been associated with nearly 50% reduction in the risk of death.[28]

In conclusion, the results of our pooled analysis highlight that platelet volume is very frequently increased in COVID-19 patients with severe illness, especially in those at higher risk of dying, such that routine measurement of MPV along with other useful laboratory parameters[29,30] should be considered for identifying those cases at higher risk of adverse progression, needing more assiduous and even more aggressive care.

Conflict of Interest
None declared.

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