Review

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Platelet distribution width (PDW) as a significant correlate of COVID-19 infection severity and mortality

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Abstract: SARS-CoV-2 infection may cause a wide spectrum of symptoms, from asymptomatic, to mild respiratory symptoms and life-threatening sepsis. Among the clinical laboratory biomarkers analyzed during COVID-19 pandemic, platelet indices have raised great interest, due to the critical involvement of platelets in COVID-19-related thromboinflammation. Through an electronic literature search on MEDLINE, CINAHL, PubMed, EMBASE, Web of Science, and preprint servers we performed and updated a systematic review aimed at providing a detailed analysis of studies addressing the potential clinical utility of platelet distribution width, platelet distribution width (PDW), in laboratory medicine, exploring the possible association between increased PDW levels, disease severity, and mortality in COVID-19. Our systematic review revealed a wide heterogeneity of COVID-19 cohorts examined and a lack of homogenous expression of platelet indices. We found that 75 % of studies reported significantly elevated PDW values in COVID-19 infected cohorts compared to healthy/non-COVID-19 controls, and 40 % of studies reported that patients with severe COVID-19 showed increased PDW values than those with less-than-severe illness. Interestingly, 71.4 % of studies demonstrated significant increased PDW values in non survivors vs. survivors. Overall, these results suggest that platelets are critically involved as major players in the process of immunothrombosis in COVID-19, and platelet reactivity and morphofunctional alterations are mirrored by PDW, as indicator of platelet heterogeneity. Our results confirm that the use of PDW as prognostic biomarkers of COVID-19 sepsis still remains debated due to the limited number of studies to draw a conclusion, but new opportunities to investigate the crucial role of platelets in thromboinflammation are warranted.

Keywords: COVID-19; platelet; platelet distribution width; PDW; SARS-CoV-2; systematic review

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Introduction

The novel coronavirus disease 2019 (COVID-19) is a pandemic infectious disease sustained by a member of the Coronaviridae family, finally called acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The range of clinical pictures is quite heterogeneous, with most patients experiencing only mild respiratory symptoms or being asymptomatic, especially among young children, with a relevant role in spreading the disease [1]. The proportion of patients with COVID-19 who progress towards severe or even critical illness, requiring sub-intensive or intensive care varies but is decreasing over time, in line with the increased population immunity, improved early diagnostic procedures, and advanced therapeutic strategies. Accordingly, the death rate is highly variable worldwide depending on genetic, epigenetic, and environmental factors [2].

Among the plethora of clinical laboratory biomarkers and potential hematological parameters analyzed during COVID-19 pandemic [3, 4], particular attention has been

focused on platelet functions and activities, as well as platelet-linked laboratory indices, due to a great deal of information available in COVID-19 patients suggesting the hyper-activation of coagulative cascade, finally leading to thrombosis and thrombocytopenia [5–8]. Interestingly, these studies shed light also on the missing pieces of the intricate puzzle of COVID-19.

According to the widely accepted association between platelet parameters and COVID-19, several recent studies on the diagnostic and prognostic value of routine hemocytometry markers underlined the clinical usefulness of platelet distribution width (PDW) in COVID-19, emphasizing the role of this measure for distinguishing and stratifying the risk of developing critical illness and/or dying. To this end, the hematological parameter PDW, linked to heterogeneity of platelet volume, has recently emerged as a predictive factor of multiorgan dysfunction, enhanced micro-thrombotic processes and increased risk of death in several physio-pathological conditions [9–12].

According to standard hematological procedures, PDW is generated alongside other platelet volume indices (mean platelet volume, MPV; plateletcrit, PCT) and represents a parameter mathematically based on the measure of platelet volume and standard deviation of volume distribution within the platelet population. In fact, PDW is an indicator of heterogeneity in platelet size, reflecting morphologic changes in reactive/activated/giant platelet cells [13, 14].

In a general perspective, higher PDW values are associated with a wider range of platelet size, which could result from platelet activation processes, platelet destruction mechanisms, or platelet consumption [13, 15–17].

Thrombotic events and hypercoagulability are also associated with increased PDW values due to the high number of platelets being destroyed and consumed (thrombocytopenia), and the activation of thrombopoiesis, which stimulates the release of younger and larger platelets from the bone marrow in the blood circulation [5, 6].

On these bases, this parameter enhances the attainment of crucial details through classic optical microscopic evaluation of peripheral blood smears, providing further crucial information on heterogeneity and volume modifications of platelets upon massive inflammo-thrombotic processes.

We describe here the results of an updated systematic review aimed to provide a detailed analysis of studies that have addressed the potential clinical utility of PDW in routine laboratory medicine, exploring the possible association between increased PDW levels, disease severity, and mortality in COVID-19 patients.

Methods

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement of 2020. As this manuscript is a systematic review, no Ethical Committee approval was required.

Search strategy

Electronic literature searches were conducted by two different authors on the following databases: MEDLINE, CINAHL, PubMed, EMBASE, and Web of Science databases, as well as on preprint servers medRxiv and bioRxiv, for studies published between 2020 and present time (i.e., latest search date: December 2, 2022). Database search strategies were conducted with the assistance of an experienced health science librarian. We also screened the reference list of identified papers for capturing black literature. Searches were limited to human studies and English language citations by using the following combinations of terms: “COVID-19” OR “SARS-CoV-2”, “platelet distribution width”, “severity”, “mortality”, “pregnancy”, “pulmonary embolism”, “acute respiratory distress syndrome”. The search strategy combined these terms using Boolean operators for the main databases is detailed in Table 1.

Selection criteria

This review included observational cohort, cross-sectional, and case-control studies. A series of comparisons were made: infected vs. uninfected healthy controls; severe vs. non-severe disease; non-survivors vs. survivors. Severe disease was clinically defined as patients needing intensive care unit (ICU) admission, mechanical (forced) ventilation, COVID-19 related hospitalization, pneumonia, or onset of critical symptoms and/or shock and/or presence of organ failure. Due to lack of comparable data between multiple studies, pediatric populations were excluded from analysis and only adult populations were considered. All studies fulfilling these criteria were then included in a systematic literature review.

Two authors reviewed the title and abstract of those publications identified in databases. Duplicates were then removed. The title and abstract were screened for eligibility and posterior full-read text. The reference list of the documents included in our analysis was also scrutinized with forward and backward citation tracking to detect other potentially eligible studies (Figure 1).

Table 1: Database formula during literature search.

PubMed, MEDLINE/CINAHL (via EBSCO), WOS (EMBASE)/Web of Science search formula
((“COVID-19)” OR “SARS-CoV-2” AND (“platelet distribution width”)) AND ((“severity”) OR (“pregnancy”) OR (“pulmonary embolism”) OR (“acute respiratory distress syndrome”))

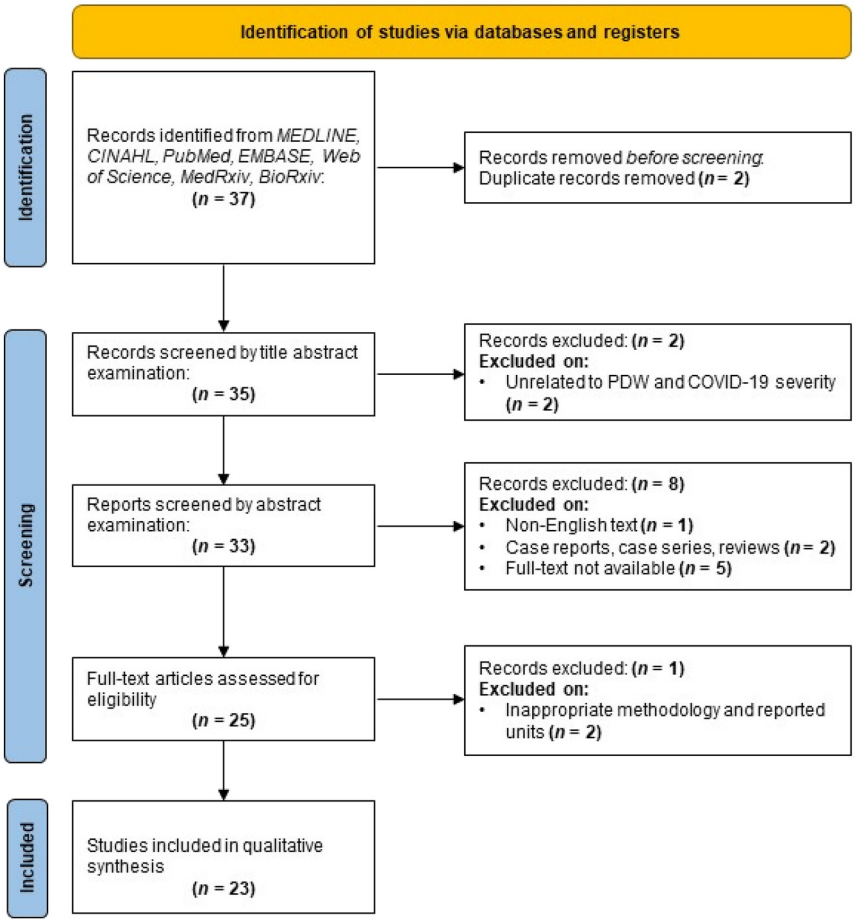

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

Data collection

Data including authors, years, country, sample size, PDW measurements (in % and femtoliters, fL) and their associated p-values were extracted from each study. Disagreements between authors with respect to study eligibility were resolved by discussion and consensus among authors, and discrepancies between reviewers at any stage of the screening process were resolved by asking a third author when necessary.

Quality assessment

The NIH Quality Assessment Tool was used to evaluate all studies used for analysis. Two authors grouped the studies into two categories: case-control studies (Table 2) and observational cohort/cross-sectional studies (Table 3). The same two authors assessed each study using the provided checklist to characterize the quality of the papers. Case control studies were evaluated by research question, study population, target population and case representation, sample size justification, groups recruited from the same population, inclusion and exclusion criteria prespecific and applied uniformly, case and control definitions, random selection of study participants, concurrent controls, exposure accessed prior to outcome measurement, exposure measures and assessment, blinding of exposure assessors, and statistical analysis parameters, where applicable. Observational cohort/cross-sectional studies were evaluated by research question, study population, groups recruited from the same population, sample size justification, exposure accessed prior to outcome measurement, sufficient timeframe to see an effect, different levels of the exposure of interest, exposure measures and assessment, repeated exposure assessment, outcome measures,

Table 2: NIH Quality Assessment Tool for evaluating case-control studies.

Case-control study	Overall quality rating	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Al-Buthabhak [18]	Good	Y	Y	Y	Y	Y	Y	N/A	N	Y	Y	N/A	N
Alnor [19]	Good	Y	Y	N	Y	Y	Y	N/A	Y	Y	Y	N/A	N/A
AydinyiImaz [20]	Good	Y	Y	Y	Y	Y	Y	N/A	N	Y	Y	N/A	Y
Nori [21]	Good	Y	Y	N	Y	Y	Y	N/A	Y	Y	Y	N/A	Y
Shankaralingappa [22]	Good	Y	Y	N	Y	Y	Y	N/A	Y	Y	Y	N/A	N/A
Yovchevska [23]	Good	Y	Y	N	Y	Y	N	N/A	Y	Y	Y	N/A	Y

Y, yes; N, not; N/A, not applicable.

Table 3: NIH Quality Assessment Tool for evaluating observational cohort and cross-sectional studies.

Observational cohort/ cross-sectional study	Overall quality rating	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Asrie [24]	Fair	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	N/A	N/A	Y
Bommenahalli Gowda [25]	Fair	Y	Y	N/A	Y	N	Y	Y	N/A	Y	N	Y	N/A	N/A	N
Suarez Castillejo [26]	Good	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	N/A	Y	N
Çelikkol [27]	Fair	Y	Y	N/A	N/A	N	Y	Y	Y	Y	N	Y	N/A	N/A	N
Covali [28]	Fair	Y	Y	Y	Y	N	Y	Y	N/A	Y	N	Y	N/A	N/A	N
Güçlü [12]	Good	Y	Y	N/A	Y	N	Y	Y	Y	Y	Y	Y	N/A	Y	N
Hajian [29]	Good	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N/A	N/A	N
Khalid [30]	Good	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N/A	N/A	Y
László [31]	Fair	Y	Y	N/A	Y	N	Y	Y	Y	Y	N	Y	N/A	N/A	N
Ouyang [32]	Fair	Y	Y	N/A	N	N	Y	Y	Y	Y	Y	Y	N/A	N/A	N
Ozcelik [33]	Fair	Y	Y	N/A	Y	N	Y	Y	N	Y	N	Y	N/A	N/A	N
Pujani [34]	Fair	N	Y	N/A	Y	N	Y	Y	Y	Y	N	Y	N/A	N/A	N
Ravindra [35]	Fair	N	Y	N/A	N/A	N	N	Y	Y	Y	N	Y	N/A	N/A	Y
Suliman [36]	Fair	Y	Y	Y	Y	N	Y	Y	N/A	N/A	N	Y	N/A	N/A	N
Wang [10]	Fair	N	Y	N/A	Y	N	Y	Y	N	N/A	N	Y	N/A	N/A	N
Ye [37]	Good	N	Y	N/A	Y	N	Y	Y	Y	Y	N	Y	N/A	N/A	Y
Zhong [38]	Good	N	Y	Y	Y	Y	Y	Y	N	N/A	Y	Y	N/A	Y	Y

Y, yes; N, not; N/A, not applicable.

blinding of outcome assessors, follow up rate, statistical analysis parameters, where applicable. Studies that achieved 75 % of the criteria or above received a score of "good"; 50 % of the criteria or above received a score of "fair"; less than 50 % of the criteria received a score of "poor".

Results

Study selection

Twenty-three studies with a total population of n=12,767 participants were selected in this systematic review to quantify platelet distribution width (PDW) in patients with COVID-19. The studies were conducted in the following countries: Iraq [18, 21], Turkey [12, 20, 27, 33], Spain [26], Romania [28], India [22, 25, 34, 35], Iran [29], Hungary [31], China [10, 32, 37, 38], Saudi Arabia [30, 36], Denmark [19], Ethiopia [24], and Bulgaria [23]. The patients were further divided into study-specific groups such as non-severe (n=778, including mild and moderate), and severe (n=510) COVID-19 cohorts; survivor (n=1,270) and non-survivor (n=360) cohorts; and presence of comorbidities including acute respiratory distress syndrome, influenza, pulmonary embolism, multisystem inflammatory system, and pneumonia. It is also worth noting that articles under these categories were nonexclusive, as many studies included more than one factor in their analysis.

Meta-analysis was not deemed appropriate due to the high heterogeneity between studies. In accordance with the guidelines outlined in the Cochrane Handbook and best practices in evidence synthesis, we did not to perform a meta-analysis due to the presence of methodological and clinical heterogeneity that cannot be adequately addressed by statistical methods alone.

By acknowledging the limitations imposed by high heterogeneity, we aimed to ensure the robustness and reliability of our findings, and to avoid combining studies with such significant differences that could introduce bias or distort the overall conclusions of the analysis.

Accordingly, we conducted a synthesis of the data reported by addressing population, patient level differences, limitations with different assays, sensitivities, and reported units, and methodological quality.

Study assessment

All studies used for analysis received scores of either good or fair. No studies received a score of poor. The studies that were deemed good include [12, 18–23, 26, 29, 30, 37, 38].

The studies that were classified as fair include [10, 24, 25, 27, 28, 31–36]. These characterizations are provided in Tables 2 and 3.

PDW trends

As reported in Tables 4 and 5, six out of eight (75 % of studies) reported significantly elevated PDW (expressed as fL or %) values in COVID-19 infected cohorts as compared to healthy

Table 4: PDW (%) in COVID-19 patients.

Author Country of origin Design	Sample size	PDW measurement	PDW significance (p-value)
Çelikkol et al. [27] Turkey Retrospective cohort	Confirmed COVID-19 patients n=56 Unconfirmed COVID-19 patients n=46 Healthy patients n=30 Mild COVID-19 cohort n=31 Severe COVID-19 cohort n=25	PDW (%) Confirmed COVID-19 patients: 16.02 ± 2.96 % Unconfirmed COVID-19 patients: 15.04 ± 3.29 % Healthy patients: 14.5 ± 1.9 % Mild COVID-19 patients: 16.05 ± 3.24 % Severe COVID-19 patients: 15.98 ± 2.63 %	Confirmed vs. healthy: 0.017 Severity: 0.921
Ozcelik et al. [33] Turkey Retrospective	COVID-19 cohort n=54 Influenza cohort n=43	PDW (%), median (IQR) COVID-19 patients: 16.2 (15.9–16.6) % Influenza patients: 12.2 (10.6–14.2) %	Diagnostic (COVID-19 vs. influenza pneumonia): <0.001
Pujani et al. [34] India Prospective cross-sectional	COVID-19 cohort n=506 Non-COVID-19 cohort n=200 Mild-moderate COVID-19 cohort n=337 Severe COVID-19 cohort n=118 Very severe COVID-19 cohort n=51 Survival subclassification COVID-19 survivor cohort n=473 COVID-19 non-survivor cohort n=33	PDW (%) Total COVID-19 patients: 16.12 ± 3.6 % Non-COVID-19 patients: 15.69 ± 2.30 % Very severe COVID-19 patients: 17.43 ± 3.78 % Severe COVID-19 patients: 16.24 ± 3.51 % Moderate COVID-19 patients: 15.99 ± 3.6 % Survivors: 16.08 ± 3.64 % Non-survivors: 17.37 ± 3.00 %	Case vs. Control (COVID-19 vs. Non-COVID-19): 0.03 Severity: 0.012 Survival: 0.047
Shankaralingappa et al. [22] India Retrospective case-control	COVID-19 cohort n=199 Non-COVID-19 cohort n=198 High PDW (>25 %) subclassification COVID-19 cohort n=1 Non-COVID-19 cohort n=5	PDW (%) *Normal reference range: 0–25 %* COVID-19 patients: 15.83 ± 5.92 % Non-COVID-19 patients: 14.44 ± 2.83 %	Case vs. Control (COVID-19 vs. Non-COVID-19): 0.003 PDW>25 %: 0.101
Covali et al. [28] Romania Prospective cohort	Positive COVID-19 cohort n=46 Negative COVID-19 cohort n=411	PDW (%), mean values (and SD) on the upper line Pregnant COVID-19 positive patients at term: 16.98 ± 2.70 % Pregnant COVID-19 negative patients at term: 16.97 ± 3.17 % PDW (%), median values (quartile 1, quartile 2) on the lower line Pregnant COVID-19 positive patients at term: 16.59 (15.10, 18.41) % Pregnant COVID-19 negative patients at term: 16.63 (14.79, 18.77) %	Case vs. Control (COVID-19 vs. COVID-19 negative in pregnant women): 0.804
Aydınyılmaz et al. [20] Turkey Retrospective case-control	All patients n=5,412 Intensive care cohort n=871 Hospital ward cohort n=4,541 ASA use (+) cohort n=118 ASA use (−) cohort n=255	PDW (%), median (IQR) Total COVID-19 positive patients: 12.0 (10.8–13.5) % Intensive care: 12.8 (11.5–14.5) % Ward: 11.9 (10.7–13.3) % COVID-19 positive patients with MPV>10.45 fl and D-dimer >500.2 ng/dL in ICU: ASA use (+): 14.40 (13.2–15.08) % ASA use (−): 14.42 (12.53–15.44) %	Hospitalization for all patients: <0.001 ASA use for MPV>10.45 fl and D-dimer >500.2 ng/dL patients in ICU: 0.415

Table 4: (continued)

Author Country of origin Design	Sample size	PDW measurement	PDW significance (p-value)
Güçlü et al. [12] Turkey Retrospective cohort	Moderate COVID-19 Measurement 1: n=80 Measurement 2: n=70 Difference: n=69 Severe COVID-19 Measurement 1: n=13 Measurement 2: n=124 Difference: n=123 COVID-19 survivors Measurement 1: n=158 Measurement 2: n=147 Difference: n=146 COVID-19 non-survivors Measurement 1: n=54 Measurement 2: n=47 Difference: n=46	PDW (%), mean ± SD PDW measurement 1 Moderate COVID-19 patients: 17.37 ± 2.32 % Severe COVID-19 patients: 17.72 ± 2.52 % Survivors: 17.44 ± 2.35 % Non-survivors: 18.02 ± 2.69 % PDW measurement 2 Moderate COVID-19 patients: 17.96 ± 1.43 % Severe COVID-19 patients: 18.13 ± 1.66 % Survivors: 17.89 ± 1.55 % Non-survivors: 18.63 ± 1.56 % PDW difference (%), mean ± SD Moderate COVID-19 patients: 0.61 ± 2.34 % Severe COVID-19 patients: 0.55 ± 2.45 % Survivors: 0.46 ± 2.35 % Non-survivors: 0.93 ± 2.57 %	PDW measurement 1 Severity: 0.142 Survival: 0.040 PDW measurement 2 Severity: 0.144 Survival: 0.006 PDW difference Severity: 0.913 Survival: 0.389
Hajian et al. [29] Iran Cross-sectional	All patients n=59 Severe COVID-19 cohort n=21 Critically ill COVID-19 cohort n=38	PDW (%), median serum (IQR) All patients: 12.0 (11.0–14.0) % Severe patients: 11.70 (10.90–13.45) % Critically ill: 12.00 (11.12–14.20) %	Severity: 0.745
Ravindra et al. [35] India Retrospective single-center	Mild COVID-19 cohort n=51 Severe COVID-19 cohort n=49 COVID-19 survivor cohort n=88 COVID-19 non-survivor cohort n=12	PDW (%), mean (SD) Mild COVID-19 patients: 17.11 (7.3) % Severe COVID-19 patients: 16.47 (2.16) % COVID-19 survivors: 15.4 (2.13) % COVID-19 non-survivors: 16.5 (3.12) %	Severity: 0.064 Survival: 0.078
Bommenahalli Gowda et al. [25] India Retrospective cross-sectional	COVID-19 survivor cohort n=75 COVID-19 non-survivor cohort: n=25	PDW (%) *Normal reference range: 15–17; mean ± SD: 16.7 ± 2.7; median: 17.4; Minimum: 1.2; Maximum: 21.5* Non-survivors: 17.58 ± 2.84 % Survivors: 16.37 ± 2.59 % Testing PDW=17 % as cut off value for influence on survival ≤17.0: Non-survivors (n=21), survivors (n=42) >17.0: Non-survivors (n=4), survivors (n=33) Odds ratio (Confidence Interval) Mortality occurrence between PDW≤17.0 % and >17.0 % indices: 4.1(1.3–13.2)	Survival: 0.05 Differentiating survival with PDW=17 % cutoff: 0.012
László et al. [31] Hungary Retrospective descriptive analysis of prospectively collected data	ICU cohort n=95 Non-ICU cohort n=111 COVID-19 survivor cohort n=130 COVID-19 non-survivors n=76 COVID-19 ICU survivor cohort n=60 COVID-19 ICU non-survivors n=35	PDW (%), Median (25–75 % confidence interval) COVID-19 survivors:14.4 (11.6–45.1)% COVID-19 non-survivors: 21.4 (14.9–57.5)% ICU patients, survivors: 16.7 (12.3–57.8)% ICU patients, non-survivors: 51.5 (15.2–57.6)%	ICU stay: <0.001 ICU survival: 0.09

Table 4: (continued)

Author Country of origin Design	Sample size	PDW measurement	PDW significance (p-value)
Ouyang et al. [32] China Retrospective	COVID-19 survivor cohort n=82 COVID-19 non-survivor cohort n=25	PDW (%) *Normal reference range: 15–17* First laboratory tests COVID-19 survivors: 16.18 % COVID-19 non-survivors: 16.63 % Last laboratory tests COVID-19 survivors: 16.14 % COVID-19 non-survivors: 16.74 %	First laboratory tests Survival: <0.001 Last laboratory tests Survival: <0.001
Al-Buthabhak et al. [18] Iraq Retrospective case-control	Mild pneumonia (no hospital admission) n=64 Moderate-severe pneumonia ICU admission n=24 Mechanical ventilation n=22 In-hospital death n=9 Complete recovery (no persistent symptoms) n=54 Post-recovery shortness of breath (O_2 dependent) n=23 Post-recovery fatigue n=19	PDW (%) COVID positive patients: 12.6 ± 2 % Odds ratio (Confidence Interval) High PDW: 0.3 (0.4–1.9)	Length of ICU stay: <0.00 Length of hospital stay: <0.00 Degree of lung injury: 0.25 Mechanical ventilation use: 0.12 In-hospital death: 0.13 Complete recovery: 0.08 Post-recovery shortness of breath (O_2 dependent): 0.07 Post-recovery fatigue: 0.05 Length of ICU stay with high PDW: <0.00
Suarez Castillejo et al. [26] Spain Prospective cohort, single-center	All patients n=179 Non-PE COVID-19 cohort n=108 PE COVID-19 cohort n=71	PDW(%) All patients Baseline: 16.3 (15.8–16.8) % Peak: 17.2 (16.9–17.9) % Prior to CTPA: 16.4 (15.9–16.8) % Non-PE COVID-19 patients Baseline: 16.1 (15.7–16.8) % Peak: 17.1 (16.8–17.7) % Prior to CTPA: 16.2 (15.8–16.7) % PE COVID-19 patients Baseline: 16.6 (16.1–17.2) % Peak: 17.3 (16.9–18.2) % Prior to CTPA: 16.6 (16.1–16.9) %	Non-PE COVID-19 patients vs. PE COVID-19 patients Baseline: 0.00 Peak: 0.04 Prior to CTPA: 0.0
Suliman et al. [36] Saudi Arabia Retrospective cohort	Non-COVID-19 cohort n=2,414	PDW (%) Mean Preceding Period (07/2019–04/2020): 13.18 % Mean Lockdown Period (05/2020–09/2020): 12.58 %	Diagnostic (pre-pandemic vs. lock-down): <0.001 (Unpaired t test and F test)
Zhong et al. [38] China Retrospective cohort	MPR≤7.44 cohort n=59 MPR>7.44 group n=26	PDW (%), median (IQR) MPR≤7.44 patients: 12.6 (11.8, 13.9) % MPR>7.44 patients: 14.6 (13.1, 16.8) %	Severity: 0.004

ASA, acetylsalicylic acid; ICU, intensive care unit; PE, pulmonary embolism; MPV, mean platelet volume; MPR, mean platelet volume/platelet count rate; CTPA, computed tomography pulmonary angiography.

unaffected controls or COVID-19 negative cohorts [19, 21, 22, 27, 33, 34].

One study by Covali et al. found no difference in the mean PDW between pregnant COVID-19 patients and pregnant uninfected control [28]. It is possible that this study's lack of significant findings is attributable to comparisons between pregnant cohorts. The study by Khalid et al. indicated a significantly greater median PDW level in healthy controls compared to in the COVID-19 infected cohort [30].

Table 5: PDW (fL) in COVID-19 patients.

Author Country of origin Design	Sample size	PDW measurement	PDW significance (p-Value)
Alnor et al. [19] Denmark Case-control (nested)	All patients Non-COVID-19 cohort n=228 COVID-19 cohort n=74 Severity subclassification Severe COVID-19 cohort n=16 Non-severe COVID-19 cohort n=58 Patients with CRP<100 mg/L Non-COVID-19 cohort n=54 COVID-19 cohort n=49 Severe COVID-19 cohort n=8 Non-severe COVID-19 cohort n=41	PDW (fL), median (IQR) All patients Non-COVID-19 patients: 11.2 (10.1–12.6) fL COVID-19 patients: 12.2 (10.6–13.4) fL Severe COVID patients: 13.0 (11.6–14.5) fL Non-severe COVID patients: 12.1 (10.5–13.2) fL For patients with CRP<100 mg/L Non-COVID-19 patients: 11.2 (10.2–12.53) fL COVID-19 patients: 12.3 (10.85–13.45) fL Severe COVID patients: 12.90 (11.65–14.48) fL Non-severe COVID patients: 12.20 (10.65–13.30) fL	All patients COVID-19 vs. non-COVID-19 patients: 0.003 Severe COVID-19 vs. non-severe COVID-19 patients: 0.097 Patients with CRP<100 mg/L COVID-19 vs. non-COVID-19 patients: 0.005 Severe COVID-19 vs. non-severe COVID-19 patients: 0.239
Nori et al. [21] Iraq Retrospective case control	COVID-19 cohort n=50 Non-COVID-19 cohort n=50	PDW (fL), mean ± SD/SE COVID-19 positive patients: 14.82 ± 3.18/0.46 fL COVID-19 negative patients: 13.3 ± 2.16/0.39 fL	Case vs. Control (COVID-19 vs. non-COVID-19 in pregnant women): 0.024
Khalid et al. [30] Saudi Arabia Retrospective cross-sectional	COVID-19 cohort n=487 Non-COVID-19 cohort n=300	PDW (fL), median (Min-Max) COVID-19 patients: 12.4 (8.8–23.3) fL Non-COVID-19 patients: 13.2 (10.3–22.1) fL Severity subclassification ICU COVID-19 patients: 12.9 (8.8–23.3) fL ER COVID-19 patients: 12.0 (8.8–22.6) fL Mild COVID-19 patients: 11.4 (9.5–15) fL Non-COVID-19 patients: 13.2 (10.3–22.1) fL	Case vs. Control (COVID vs. Non-COVID): 0.000 Severity: 0.000
Asrie et al. [24] Ethiopia Cross-sectional	All patients n=117 Mild COVID-19 cohort n=45 Moderate COVID-19 cohort n=43 Severe COVID-19 cohort n=29	PDW (fL), median (IQR) All patients: 16.4 (0.75) fL Mild COVID-19 patients: 16.4 (0.65) fL Moderate COVID-19 patients: 16.5 (0.7) fL Severe COVID-19 patients: 17 (1.55) fL	Severity: 0.001
Yovchevska et al. [23] Bulgaria Retrospective analytic case-control, single center	COVID-19 patients with ARDS n=190 COVID-19 patients without ARDS n=303 COVID-19 survivor cohort	PDW (fL) COVID-19 patients with ARDS: 15.10 ± 2.08 fL COVID-19 patients without ARDS: 12.94 ± 2.12 fL	Severity (ARDS): <0.001 Survival: 0.095

Table 5: (continued)

Author Country of origin Design	Sample size	PDW measurement	PDW significance (p-Value)
	n=133 COVID-19 non-survivor cohort n=57	COVID-19 survivors: 14.93 ± 2.16 fL COVID-19 non-survivors: 15.48 ± 1.84 fL	
Ye et al. [37] China Retrospective cross-sectional	Asymptomatic-moderate cohort n=132 Severe or above cohort n=29	PDW (fL) Asymptomatic-moderate patients: 14.98 ± 3.17 fL Severe and above patients: 15.34 ± 2.08 fL	Severity (asymptomatic-moderate/severe and above): 0.559
László et al. [31] Hungary Retrospective descriptive analysis of prospectively collected data	ICU cohort n=95 Non-ICU cohort n=111 COVID-19 survivor cohort n=130 COVID-19 non-survivors n=76 COVID-19 ICU survivor cohort n=60 COVID-19 ICU non-survivors n=35	PDW (fL), median (25%-75 % confidence interval) ICU patients: 19.9 (13.7–57.7) Non-ICU patients: 14.5 (11.6–44.7)	ICU stay: <0.001 ICU survival: 0.09
Wang et al. [10] China Retrospective single center	COVID-19 positive cohort n=40	PDW (fL) Admission group: 11.75 ± 1.227 fL Discharge group: 12.23 ± 1.485 fL	Diagnostic (admission vs. discharge): 0.0186

ARDS, acute respiratory distress syndrome.

Four out of ten (40 % of studies) exhibited significantly increased PDW values in patients with severe COVID-19 vs. in those with less-than-severe illness [20, 23, 24, 34]. All of the remaining studies that tested for a severity-dependent PDW correspondence do not show significance between the two groups [12, 19, 27, 29, 35, 37]. The lack of a significant difference in the study by Güçlü et al. may be a result of the narrower comparison of PDW levels from moderate-to-severe COVID-19 cohorts [12]. Similarly, the report by Hajian et al. compared PDW values in severe vs. critically ill COVID-19 cohorts – such that the differences between groups may be too small to detect a difference in PDW [29].

Five out of seven (71.4 % of studies) demonstrate a significant elevation of PDW values in patients who died from COVID-19 compared with patients who were infected with the virus but survived [12, 25, 31, 32, 34]. The remaining two studies indicated non-significant differences between the groups [23, 35].

Discussion

PDW is a laboratory test that measures volume variability in platelet size, providing an indicator of the heterogeneity in platelet morphology [14]. PDW is widely used as an indicator of platelet function and activation, and it has been reported as a more specific marker of platelet activation, since it does not increase during simple platelet swelling, suggesting higher PDW values on admission to internal medicine wards associated with a more severe clinical profile and increased risk of 90-day mortality [11].

Several reports (n=23) were analyzed by our systematic review, revealing a wide heterogeneity of population cohorts examined and a lack of homogenous expression of platelet indices (e.g., PDW was expressed as fL and percentage).

Overall, the findings of our systematic review revealed that 75 % of studies reported significantly elevated PDW values in COVID-19 infected cohorts compared to healthy/non-COVID-19 controls [19, 21, 22, 27, 33, 34], and that 40 % of studies reported that patients with severe COVID-19 showed increased PDW values than those with less-than-severe illness [20, 23, 24, 34]. However, the lack of a significant difference in some studies may depend on the different selection of COVID-19 cohorts among studies.

In fact, stratifying patients according to their survival, we observed that 71.4 % of studies demonstrated a

significant increase of PDW values in patients who died from COVID-19 compared with patients who were infected with the virus but survived [12, 25, 31, 32, 34].

Overall, these results suggest that during Sars-Cov-2 infection platelets are critically involved as major players in the process of immunothrombosis. Platelet reactivity is mirrored by morphofunctional alterations, such as increased MPV and PDW, as indicators of platelet heterogeneity.

Several studies reported that platelets tend to be deformed, to became giant, to form homotypic and heterotypic aggregates, which finally results in a thrombocytopenic condition induced by platelet destruction or consumption, associated with the release of younger and larger platelets from the bone marrow, overall contributing to increased PDW values [5, 6, 13, 15–17].

A similar scenario has also been described to be induced by high levels of circulating histones, which represent critical triggers found at increased concentration in blood samples from COVID-19 and sepsis patients, recognized to be able to induce a thrombocytopenic condition and platelet heterogeneity [39]. Notably, possible heterogeneity in hematological procedures applied for analysis of PDW may also impact the compatibility of PDW data among studies and the conclusions made on present PDW trends. Finally, despite several studies indicating increased PDW values in COVID-19, our results confirm that the use of PDW as possible prognostic biomarkers of COVID-19 sepsis still remains debated due to the limited number of studies to draw a conclusion [40], but new opportunities to investigate the crucial role of platelets in thrombo-inflammation are guaranteed. In this respect, the use of PDW could implement the everyday clinical practice if included in various artificial intelligence (AI) algorithms [41, 42], contributing to the development of innovative diagnostic and prognostic approaches.

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References

1. Dobrijević D, Katanić J, Todorović M, Vučković B. Baseline laboratory parameters for preliminary diagnosis of COVID-19 among children: a cross-sectional study. Sao Paulo Med J 2022;140:691–6.
2. Bell TD. COVID-19 in the critically ill patient. Infect Dis Clin North Am 2022;36:365–77.
3. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med 2020;58:1063–9.
4. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020;58:1021–8.
5. Ahmadi E, Bagherpour Z, Zarei E, Omidkhoda A. Pathological effects of SARS-CoV-2 on hematological and immunological cells: alterations in count, morphology, and function. Pathol Res Pract 2022;231: 153782.
6. Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. Pathobiology 2021;88:15–27.
7. Palladino M. Complete blood count alterations in COVID-19 patients: a narrative review. Biochem Med 2021;31:030501.
8. Comer SP, Cullivan S, Szklanna PB, Weiss L, Cullen S, Kelliher S, et al. COVID-19 induces a hyperactive phenotype in circulating platelets. PLoS Biol 2021;19:e3001109.
9. Yardımcı AC, Yıldız S, Ergen E, Ballı H, Ergene E, Guner YS, et al. Association between platelet indices and the severity of the disease and mortality in patients with COVID-19. Eur Rev Med Pharmacol Sci 2021;25:6731–40.
10. Wang Y, Fan Z, Wang S, Zhuang C. The diagnostic value of platelet distribution width in patients with mild COVID-19. J Clin Lab Anal 2021; 35:e23703.
11. Tzur I, Barchel D, Izhakian S, Swarka M, Garach-Jehoshua O, Krutkina E, et al. Platelet distribution width: a novel prognostic marker in an internal medicine ward. J Community Hosp Intern Med Perspect 2019; 9:464–70.
12. Güçlü E, Kocayiğit H, Okan HD, Erkorkmaz U, Yürümez Y, Yaylacı S, et al. Effect of COVID-19 on platelet count and its indices. Rev Assoc Med Bras 2020;66:1122–7.
13. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia 2010;14:28–32.
14. Gao Y, Li Y, Yu X, Guo S, Ji X, Sun T, et al. The impact of various platelet indices as prognostic markers of septic shock. PLoS One 2014;9:e103761.
15. Kamisli O, Kamisli S, Kablan Y, Gonullu S, Ozcan C. The prognostic value of an increased mean platelet volume and platelet distribution width in the early phase of cerebral venous sinus thrombosis. Clin Appl Thromb Hemost 2013;19:29–32.
16. Sevuk U, Bahadir MV, Altindag R, Baysal E, Yaylak B, Ay N, et al. Value of serial platelet indices measurements for the prediction of pulmonary embolism in patients with deep venous thrombosis. Therapeut Clin Risk Manag 2015;11:1243–9.
17. Ulucan Ş, Keser A, Kaya Z, Katlandur H, Özdil H, Bilgi M, et al. Association between PDW and long term major adverse cardiac events in patients with acute coronary syndrome. Heart Lung Circ 2016;25:29–34.
18. Al-Buthabhak K, Nafakhi H, Shukur MH, Nafakhi A, Alareedh M, Shaghee F. Blood indices, in-hospital outcome and short-term prognosis in patients with COVID-19 pneumonia. Monaldi Arch Chest Dis 2021. https://doi.org/10.4081/monaldi.2021.1782.
19. Alnor A, Sandberg MB, Toftanes BE, Vinholt PJ. Platelet parameters and leukocyte morphology is altered in COVID-19 patients compared to non-COVID-19 patients with similar symptomatology. Scand J Clin Lab Invest 2021;81:213–7.
20. Aydınyılmaz F, Aksakal E, Pamukcu HE, Aydemir S, Doğan R, Saraç İ, et al. Significance of MPV, RDW and PDW with the severity and

mortality of COVID-19 and effects of acetylsalicylic acid use. Clin Appl Thromb Hemost 2021;27:10760296211048808.
21. Nori W, Hameed BH, Thamir AR, Fadhil A. COVID-19 in pregnancy: implication on platelets and blood indices. Rev Bras Ginecol Obstet 2021;43:595–9.
22. Shankaralingappa A, Tummidi S, Arun Babu T. Diagnostic value of platelet indices in COVID 19 infection: a case-control study from a single tertiary care center. Egypt J Intern Med 2022;34:35.
23. Yovchevska IP, Trenovski AB, Atanasova MH, Georgiev MN, Tafradjiiska-Hadjiolova RK, Lazarov SD, et al. Platelet distribution width and increased D-dimer at admission predicts subsequent development of ARDS in COVID-19 patients. Pathophysiology 2022; 29:233–42.
24. Asrie F, Tekle E, Gelaw Y, Dagnew M, Gelaw A, Negash M, et al. Baseline thrombocytopenia and disease severity among COVID-19 patients, tibebe ghion specialized hospital COVID-19 treatment center, northwest Ethiopia. J Blood Med 2022;13:315–25.
25. Bommenahalli Gowda S, Gosavi S, Ananda Rao A, Shastry S, Raj SC, Menon S, et al. Prognosis of COVID-19: red cell distribution width, platelet distribution width, and C-reactive protein. Cureus 2021;13:e13078.
26. Suarez Castillejo C, Toledo-Pons N, Calvo N, Ramon-Clar L, Martínez J, Hermoso de Mendoza S, et al. A prospective study evaluating cumulative incidence and a specific prediction rule in pulmonary embolism in COVID-19. Front Med 2022;9:936816.
27. Çelikkol A, Güzel E, Doğan M, Erdal B, Yilmaz A. C-reactive protein-to-albumin ratio as a prognostic inflammatory marker in COVID-19. J Lab Physicians 2022;14:74–83.
28. Covali R, Socolov D, Socolov R, Pavaleanu I, Carauleanu A, Akad M, et al. Complete blood count peculiarities in pregnant SARS-CoV-2-infected patients at term: a cohort study. Diagnostics 2021;12:80.
29. Hajian S, Sarbazi-Golezari A, Karbasi M, Oveisi S, Ahmadi MH, Sotoudeh M, et al. Evaluation of the relation between disease severity with platelet distribution width, platelet large cell ratio, mean platelet volume and red cell distribution width in severe and critically ill hospitalized patients with coronavirus disease 2019. J Parathyr Dis 2022;10:e10156.
30. Khalid A, Suliman AM, Abdallah EI, Abakar MAA, Elbasheir MM, Muddathir AM, et al. Influence of COVID-19 on lymphocyte and platelet parameters among patients admitted to intensive care unit and emergency. Eur Rev Med Pharmacol Sci 2022;26:2579–85.
31. László I, Berhés M, Tisza K, Miltényi Z, Balázsfalvi N, Vaskó A, et al. The prognostic value of laboratory parameters referring to hemopoietic stress in patients with COVID-19—a single center experience. Signa Vitae 2023;19:36–43.
32. Ouyang SM, Zhu HQ, Xie YN, Zou ZS, Zuo HM, Rao YW, et al. Temporal changes in laboratory markers of survivors and non-survivors of adult inpatients with COVID-19. BMC Infect Dis 2020;20:952.
33. Ozcelik N, Ozyurt S, Yilmaz Kara B, Gumus A, Sahin U. The value of the platelet count and platelet indices in differentiation of COVID-19 and influenza pneumonia. J Med Virol 2021;93:2221–6.
34. Pujani M, Raychaudhuri S, Verma N, Kaur H, Agarwal S, Singh M, et al. Association of Hematologic biomarkers and their combinations with disease severity and mortality in COVID-19- an Indian perspective. Am J Blood Res 2021;11:180–90.
35. Ravindra R, Ramamurthy P, Aslam SS, Kulkarni A, Suhail K, Ramamurthy PS. Platelet indices and platelet to lymphocyte ratio (PLR) as markers for predicting COVID-19 infection severity. Cureus 2022;14:e28206.
36. Suliman BA. Dynamics of COVID-19 lockdown on blood indices and its impact on individuals' immunological health status: a cohort study in madinah, Saudi Arabia. J Blood Med 2021;12:395–402.
37. Ye J, Hua M, Zhu F. Machine learning algorithms are superior to conventional regression models in predicting risk stratification of COVID-19 patients. Risk Manag Healthc Policy 2021;14:3159–66.
38. Zhong Q, Peng J. Mean platelet volume/platelet count ratio predicts severe pneumonia of COVID-19. J Clin Lab Anal 2021;35:e23607.
39. Giglio RV, Ligi D, Della Franca C, Lo Sasso B, Rivas JZ, Agnello L, et al. Thrombocytopenia and hyperinflammation are induced by extracellular histones circulating in blood. Clin Chem Lab Med 2023;61: e239–43.
40. Daniels S, Wei H, van Tongeren M, Denning DW. Are platelet volume indices of clinical use in COVID-19? A systematic review. Front Cardiovasc Med 2022;9:1031092.
41. Dobrijević D, Antić J, Rakić G, Katanić J, Andrijević L, Pastor K. Clinical hematochemical parameters in differential diagnosis between pediatric SARS-CoV-2 and influenza virus infection: an automated machine learning approach. Children 2023;10:761.
42. Dobrijević D, Andrijević L, Antić J, Rakić G, Pastor K. Hemogram-based decision tree models for discriminating COVID-19 from RSV in infants. J Clin Lab Anal 2023;37:e24862.