Red Blood Cell Distribution Is a Significant Predictor of Severe Illness in Coronavirus Disease 2019

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Abstract

Introduction: As red blood cell distribution width (RDW) significantly predicts clinical outcomes in patients with respiratory tract infections and in those with critical illnesses, we performed a critical analysis of the literature to explore the potential prognostic role of this laboratory parameter in coronavirus disease 2019 (COVID-19). ***Methods:*** An electronic search was conducted in Medline, Scopus and Web of Science, using the keywords "coronavirus disease 2019" OR "COVID-19" AND "red blood cell distribution width" OR "RDW" in all fields, up to the present time, with no language restriction. Studies reporting the value of RDW-CV in COVID-19 patients with or without severe illness were included in a pooled analysis. ***Results:*** The pooled analysis included 3 studies, totaling 11,445 COVID-19 patients' samples (2,654 with severe disease; 23.2%). In all investigations RDW-CV was higher in COVID-19 patients with severe illness than in those with mild disease, with differences between 0.30 and 0.70%. The pooled analysis, despite consistent heterogeneity (I^2: 88%), revealed that the absolute RDW-CV value was 0.69% higher (95% CI 0.40–0.98%; $p < 0.001$) in COVID-19 patients with severe illness compared to those with mild disease. ***Conclusion:*** These results, along with data published in other studies, support the use of RDW for assessing the risk of unfavorable COVID-19 progression.

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Introduction

Coronavirus disease 2019 (COVID-19), the pandemic infectious disease sustained by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread unrelentingly around the world, being responsible for thousands of deaths each day. Despite the fact that SARS-CoV-2 is a predominantly respiratory pathogen, COVID-19 progresses as a multiple-phase and multifactorial disorder where an initial lung involvement is then accompanied by a systemic immunoinflammatory reaction (i.e., immunothrombosis), which culminates in the

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risk of developing thrombosis, with lung (i.e., acute respiratory distress syndrome; ARDS) and distant multiple-organ injury [1, 2].

According to recent data, an unfavorable progression of SARS-CoV-2 infection, such as needing mechanical ventilation and intensive care unit (ICU) admission, occurs in over 30% of patients, and it is then associated with a mortality rate approximating 40% [3]. Therefore, the identification of demographic, clinical, radiological, and laboratory predictors of unfavorable disease progression must be considered a priority for current clinical and translational research on COVID-19, as this will enable a timely, tailored, and more aggressive treatment for those patients who may have an increased risk of developing severe or critical disease.

Anisocytosis is currently defined as a biological condition characterized by circulating erythrocytes with pronounced volume heterogeneity (i.e., large, small, or both) [4]. This parameter is typically expressed as red blood cell distribution width (RDW) and can hence be calculated as the SD of the mean corpuscular volume (RDW-SD) or – more frequently – as the coefficient of variation of erythrocyte volumes (RDW-CV) as follows: RDW-CV = SD of erythrocyte volumes/mean corpuscular volume × 100 [4].

There is already consolidated evidence that the measurement of RDW represents a valuable aid for diagnosing, prognosticating, monitoring, and guiding the therapeutic management of a kaleidoscope of human pathologies [5, 6], including critical illnesses [7]. An inspired meta-analysis, published by Zhang et al. [8], recently showed that an RDW value exceeding its diagnostic threshold is a significant and independent predictor of mortality in patients with respiratory tract infections (HR = 1.15; 95% CI 1.10–1.20). This analysis confirmed similar findings in critically ill patients undergoing mechanical ventilation in the ICU [9] and persuaded us to perform a critical analysis of the current scientific literature to explore the potential prognostic role of this laboratory parameter in COVID-19.

Materials and Methods

We conducted an electronic search in Medline (PubMed interface), Scopus, and Web of Science, using the keywords "coronavirus disease 2019" OR "COVID-19" AND "red blood cell distribution width" OR "RDW" in all fields, up to the present time (i.e., July 17, 2020), with no language restrictions. The title, abstract, and full text of all identified documents were analyzed for inclusion by 2 independent reviewers, and those reporting the value of RDW-CV in COVID-19 patients with or without severe illness (i.e., in those developing severe respiratory failure, needing me-

chanical ventilation or intensive care, or those who died) were finally included in a pooled analysis. No inter-reviewer disagreements occurred. The references of all documents were also scrutinized (using forward and backward citation tracking), with the purpose of identifying other eligible studies. A pooled analysis was finally performed, encompassing the calculation of weighted mean difference and its 95% CI of RDW-CV values in COVID-19 patients with or without severe illness. When the mean value and the SD of RDW-CV were not immediately available, these measures were extrapolated from sample size, median, and IQR, as suggested by Hozo et al. [10]. A random-effects model was applied to adjusting potential heterogeneity emerging from different value thresholds and methods across the different investigations. Heterogeneity was evaluated with the χ^2 test and I^2 statistics. The meta-analysis was carried out using MetaXL software version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, QLD, Australia), while significance of difference between cumulative RDW values has been calculated from the individual mean, SD, and sample size values using MedCalc (MedCalc Software Ltd., Ostend, Belgium). This study was performed in accordance with the declaration of Helsinki and within the terms of the local legislation.

Results

Overall, 13 documents could be initially identified based on our search criteria, 10 of which were excluded after title, abstract, or full-text reading because they did not include RDW data ($n = 4$), did not directly compare RDW values between severe and nonsevere COVID-19 cases ($n = 2$), were review articles ($n = 2$), only described a study protocol ($n = 1$), or described a single case ($n = 1$). Therefore, the pooled analysis finally included 3 studies [11–13], totaling 11,445 samples collected from COVID-19 patients (2,654 with severe disease; 23.2%, range 14.8–23.4%) (Table 1). Severe COVID-19 cases were classified as respiratory failure in 2 studies [11, 13] and death in 1 study [12]. Two studies were performed in China [11, 13] and the remaining was conducted in the USA [12]. No detailed information was provided on the analytical techniques and/or instruments used for measuring RDW in any of the studies. The final sample size consisted of 11,095 COVID-19 patients from the study of Levy et al. [12], 189 patients from the study by Gong et al. [11], and 161 samples from the study by Wang et al. [13]. Further details on patient characteristics are presented in Table 1. No risk of bias or level of evidence assessment could be performed due to the limited number of available studies.

The results of the single studies are shown in Table 1 and Figure 1. In all 3 separate analyses, the RDW-CV values were found to be higher in COVID-19 patients with severe illness than in those with mild disease, with differences between 0.30 and 0.70%. The pooled analysis, de-
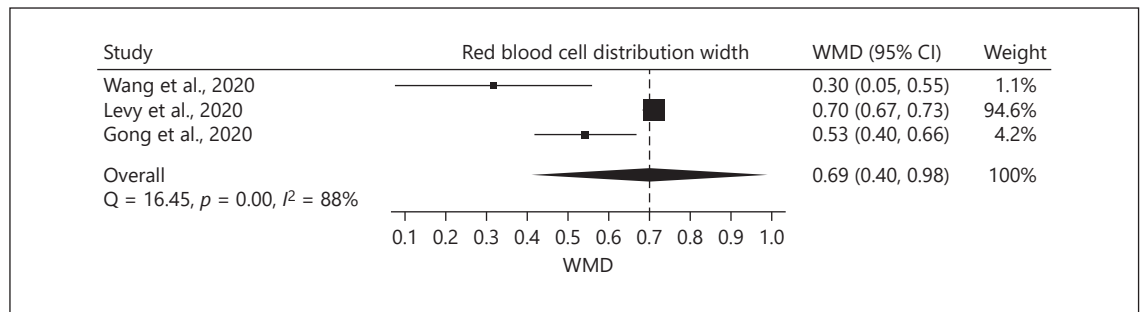
Fig. 1. Difference between RDW and RDW-CV values, expressed as a weighed mean difference (WMD) (95% CI), between COVID-19 patients with or without severe illness [11–13].

Table 1. Main characteristics of the studies included in the pooled analysis

Study	Setting	Blood sample size, n (% females)	Age, years	Severe disease, %	RDW in severe vs. nonsevere disease, %
Gong et al. [11]	China	189 (48.1)	49±8	14.8	12.75±0.31 vs. 12.22±0.33 ($p < 0.01$)
Levy et al. [12]	USA	11,095 (41.3)	65±7	23.4	14.20±0.77 vs. 13.50±0.31 ($p < 0.001$)
Wang et al. [13]	China	161 (48.9)	39±13	18.6	12.59±0.65 vs. 12.29±0.46 ($p = 0.02$)
Cumulative value	–	–	–	–	14.17±0.55 vs. 13.48±0.36 ($p < 0.001$)

Values are presented as means ± SD unless otherwise stated. RDW, red blood cell distribution width.

spite consistent heterogeneity mostly attributable to a large variation in sample size ($I^2 = 88\%$), revealed that the absolute RDW-CV value was 0.69% higher (95% CI 0.40–0.98%; $p < 0.001$) in COVID-19 patients with severe illness than in those with mild disease, thus reflecting a 1.05-fold (95% CI 1.03- to 1.08-fold) increase in severe COVID-19 cases.

Discussion

Predicting the clinical trajectory of COVID-19 is a primary area of current research, whereby earlier and targeted (personalized) therapeutic management of patients with SARS-CoV-2 infection at a higher risk of progressing toward unfavorable outcomes would generate paramount clinical, societal, and economic benefits [14]. Several laboratory parameters have been previously identified for assisting in risk stratification of development of several COVID-19 illnesses [1, 15]. Some of these are conventional hematological parameters, such as leukocytosis, lymphopenia, thrombocytopenia, and even anemia. Each of these tests reflects a different deranged pathway

in the pathogenesis of COVID-19, which requires specific clinical attention and/or management.

An increased RDW value, which mirrors a large burden of anisocytosis in circulating erythrocytes, is now universally considered a strong and independent marker of many different RBC abnormalities that can be encountered in a vast array of human disorders [16]. Notably, some previous studies have found that increased RDW is associated with mortality in patients with nonspecific ARDS (i.e., without COVID-19) [17–19]. It is thus not surprising that these earlier findings could be confirmed in this meta-analysis, which clearly shows that RDW values are significantly higher in COVID-19 patients with severe illness than in those with mild disease. This evidence was found to be consistent throughout the three clinical studies that we identified in our literature search, as well as in the final pooled analysis (Fig. 1).

It is interesting to mention here that the results of some additional COVID-19 clinical investigations, which could not be included in our analysis because they did not provide absolute RDW values, seem to be firmly aligned with these conclusions. Briefly, Foy et al. [20] studied 1,198 COVID-19 patients and found that those with an

increased RDW value at admission (i.e., >14.5%) had a 2.5-fold higher risk of in-hospital mortality compared to those with lower values (i.e., 22 vs. 9%; relative risk, 2.5; 95% CI 2.25–2.83). Moreover, an in-hospital increasing RDW was also associated with enhanced risk of death. In another study, including 294 patients hospitalized for COVID-19 [21], not only was the prevalence of increased RDW values (>14.6%) found to be considerably high (i.e., 49.7%), but also anisocytosis was associated with a 4.5-fold enhanced risk of in-hospital mortality (OR = 4.5; 95% CI 1.4–14.3) after adjustment for several covariates such as age, gender, BMI, anemia, and comorbidities. In a third clinical study, RDW was measured at admission in 84 COVID-19 patients [22], and it was found to be significantly higher in those with severe illness than in those with mild disease (absolute RDW values are not provided in the text).

With regard to the mechanistic process of RBC involvement in COVID-19, while multiple hypotheses can be formulated, the strong inflammatory dependent variation of anisocytosis represents the most likely theory. More specifically, it has been demonstrated that RDW values remarkably increase in response to many acute and chronic proinflammatory conditions [23]. It is now clear that the detrimental clinical progression of SARS-CoV-2 infection is driven by an abnormal, dysregulated, and exaggerated proinflammatory reaction, which leads to the so-called cytokine storm, now recognized as a primary trigger of lung injury and multiple organ dysfunction syndrome [2]. Many of the proinflammatory cytokines upregulated in COVID-19, including tumor necrosis factor (TNF)-α and interleukin (IL)-1, are reported to decrease erythropoietin production [24]. Secondly, RDW has been shown to be a strong predictor of adverse outcomes in patients with sepsis [25], and bacterial super-infections have a relatively high frequency in patients with severe SARS-CoV-2 illness [26]. Third, the original SARS virus was suspected to be able to directly infect hematopoietic stem/progenitor cells via CD13 or CD66a, thereby inhibiting growth and apoptosis [27]. Finally, anisocytosis in COVID-19 patients with severe illness may occur due to disrupted erythropoiesis as a result of the hypoxic disease per se, or iatrogenically, due to therapies given to these critically ill patients [28, 29]. Although it is not surprising that RDW values would strongly predict unfavorable clinical outcomes in patients with SARS-CoV-2 infection, further studies are needed to elucidate its role in the clinical course of this disease, and especially to establish whether anisocytosis shall be considered an active player or a simple bystander in COVID-19 pathophysiology.

In conclusion, despite the broad heterogeneity (i.e., $I^2 = 88\%$) found among the currently available studies, the results of our pooled analysis, along with data published in other separate studies, strongly support the use of RDW for assessing the risk of unfavorable clinical progression in patients with COVID-19. This conclusion is further supported by the evidence that RDW is a low-cost parameter compared to other measures that are more expensive and would require more cumbersome and specialized techniques. In fact, RDW is automatically generated by the vast majority of hematological analyzers, even during stat testing, and can hence be offered multiple times per day for real-time monitoring of a patient's clinical course of disease. Finally, since an increased RDW value has been shown to significantly predict patient mortality after ICU discharge [30], and the medium- and long-term clinical consequences of COVID-19 patients recovering after severe illness are still largely unknown [31], urgent studies should be planned to identify whether RDW may also be useful for predicting the post-recovery course of this disease.

Statement of Ethics

Conflict of Interest Statement

Funding Sources

Author Contributions

G.L. conceived and designed this study. G.L., B.M.H., and F.S.-G. conducted the literature search and screening. G.L., B.M.H., and F.S.-G. conducted data management. G.L., B.M.H., and F.S.-G. analyzed and interpreted the data. G.L. drafted this paper. B.M.H. and F.S.-G. participated in revision of this paper.

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