Clinical significance of changes in red cell distribution width during hospitalization for COVID-19

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Running title: RDW changes during hospitalization for COVID-19

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Abstract

Background: The possible differences in characteristics and prognosis, among patients with coronavirus disease 2019 (COVID-19), with vs. without changes in red cell distribution width (RDW) during hospitalization, have not been investigated.

Methods: For 477 adults hospitalized with COVID-19, demographic, laboratory and clinical characteristics, in-hospital outcomes and all-cause mortality were compared according: to high (>14.7%, n=146) vs. normal (≤14.7%, n=331) RDW values at admission, and according to RDW changes (n=150) vs. stable RDW (n=262) during hospitalization.

Results: Both high RDW at admission and change in RDW during hospitalization were significantly associated with older age, more severe clinical and laboratory characteristics, and poor in-hospital outcomes. On median follow-up lasting 83 days, the mortality rates were higher among patients with high vs. normal RDW on admission (26.7% vs. 10.0%, $P < .001$) and RDW changes vs. stable RDW (34.7% vs. 5.7%, $P < .001$). On multivariate analysis, change in RDW was strongly associated with decreased survival (relative risk 1.50 and 95% confidence interval 1.29–1.75), while high RDW on admission was not found to be most significantly associated with mortality.

Conclusions: Among patients with COVID-19, RDW changes during hospitalization were associated with a severe clinical profile, poor in-hospital outcomes and increased short-term mortality. Repeated assessment of RDW may provide useful information for improving the care of hospitalized patients with COVID-19.

Keywords: red cell distribution width, COVID-19, prognosis, mortality**,** hospitalization

What's known

- Coronavirus disease 2019 (COVID-19) is the pandemic infection with substantial risk of hospitalization, prolonged critical illness and death.
- Elevated levels of red cell distribution width (RDW) at hospital admission were found to be associated with more severe COVID-19 and an increased risk of in-hospital mortality.
- The possible differences in characteristics and prognosis, among patients with COVID-19 with vs. without changes in RDW during hospitalization, have not been investigated.

What's new

- Dynamic change in RDW is common among hospitalized patients with COVID-19.
- Change in RDW is associated with COVID-19 severity and poor in-hospital outcomes.
- Change in RDW predicts an increased risk of short-term mortality.
- Repeated RDW assessment may improve risk stratification for patients with COVID-19.

1 | INTRODUCTION

Red blood cell distribution width (RDW) is a coefficient of the variation in volume of circulating erythrocytes and reflects anisocytosis.[1,2] RDW is routinely measured in clinical practice as a part of complete blood count (CBC) and is traditionally used for the differential diagnosis of anemia.[1,2] However, RDW values have been shown to be increased, and to predict morbidity and mortality in many non-hematologic conditions, such as: cardiovascular diseases, inflammatory disorders and infections.[2–14] Moreover, during hospitalization for a variety of disorders, rapid changes in RDW, even within the normal range, have shown prognostic significance.[4,7,10–14]

Coronavirus disease 2019 (COVID-19) is the pandemic infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[15] COVID-19 is a common reason for hospitalization, with substantial risk of prolonged critical illness and death.[16–18] Information about the clinical significance of RDW in patients hospitalized with COVID-19 is limited. The relevant studies focused on a single evaluation of RDW at hospital admission. Elevated RDW levels were found to be associated with more severe COVID-19[19–22] and an increased risk of in-hospital mortality.[23,24] In a single study only, a prognostic significance of dynamic RDW changes among inpatients with COVID-19 was reported.[24] Patients with a rise in RDW during hospitalization had a higher risk of in-hospital mortality than did those with stable RDW values.[24] However, clinical characteristics and other outcomes of patients hospitalized with COVID-19 have not been compared between those with vs. without significant time-dependent changes in RDW. Therefore, we aimed to compare clinical characteristics, in-hospital outcomes and short-term mortality in patients with COVID-19, according to high vs. normal RDW values on admission, and according to dynamic changes in RDW during hospitalization.

2 | METHODS

2.1 | Study population and design

We conducted a retrospective observational single-center investigation. Figure 1 illustrates the design of the study. The study population comprised consecutive adult patients hospitalized with symptomatic COVID-19 in the corona facility of our tertiary university hospital during March-September 2020. The corona facility included 78 general and 12 intensive care beds. The patients were admitted from the emergency department or transferred from other departments. For patients who were readmitted, only the data of their first hospitalization were analyzed. Patients without CBC on admission were excluded from the study (Figure 1). Blood samples for measurement of RDW and other CBC parameters were drawn into ethylenediaminetetraacetic acid (EDTA) anticoagulation tubes and tested within one hour of collection by an automated UniCel Dxh hematology analyzer (Beckman Coulter A63013-AE, Inc., CA, USA).

For analysis of the association of RDW on admission with demographic, clinical and laboratory variables, and with outcomes, 477 patients were included. They were classified into groups 1 and 2, according to normal (≤ 14.7%) and high (> 14.7%) RDW values on admission, respectively. Associations of time-dependent RDW changes with outcomes and other relevant data were also analyzed. This analysis included only patients with an available CBC within 48 hours of discharge or death, and an interval between the first and last CBC of at least 3 days (Figure 1). The eligible 412 patients were classified according to ΔRDW (RDW on discharge minus RDW on admission), into groups A (non-significant RDW changes, ΔRDW ≤ ± 0.4%) and B (significant changes, a drop or rise, in RDW, ΔRDW > ± 0.4%).

During the current hospitalization, the patients were treated for COVID-19, using the standardized protocol. The protocol was approved and regularly updated by the institutional experts' board, according to information from the medical literature. The follow-up ended on October 2020. For survivors, pre-specified minimal and maximal follow-up durations were 30 and 217 days, respectively. The primary outcome was all-cause mortality. Secondary outcomes were related to the index hospitalization and included: pneumonia, nosocomial infection, acute coronary syndrome, exacerbated heart failure, stroke, venous thromboembolism, transfer to the intensive care unit, treatment with mechanical ventilation, duration of hospital stay and death. The study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional Ethics Committee (approval number 0142-20-ASF).

2.2 | Data collection

The following data were collected from electronic medical records: demographic, clinical and laboratory variables, and the in-hospital outcomes. Following discharge, vital status in the end of follow-up was registered, based on information from the registry of the Ministry of Internal Affairs.

2.3 | Definitions

The cut-off of 0.4% for ΔRDW was chosen to minimize the chance of misclassification of patients according to known normal individual RDW variability or variability of RDW measurement by the counter.[2,10,11] Renal failure was defined as any value of estimated glomerular filtration rate < 60ml/min/1.73m^2 during the index hospitalization, using the

Modification of Diet in Renal Disease equation.[25]Anemia was diagnosed according to the World Health Organization criteria: a hemoglobin concentration of < 13 g/dl in men and < 12 g/dl in women. Lymphopenia was defined as lymphocyte count below (1.0 x 10^9/l) normal range values. Pneumonia was defined as a new chest radiographic infiltrate, which was not due to another known cause.

COVID-19 was diagnosed according to qualitative detection of SARS-CoV-2 RNA in nasopharyngeal swab, which was performed using the Allplex™ 2019-nCoV assay in a CFX96™ real-time polymerase chain reaction detection system. COVID-19 was categorized as mild-moderate and severe illness on admission. The presence of clinical symptoms with or without radiographic evidence of lower respiratory tract disease, but with a blood oxygen saturation of ≥ 94% on breathing ambient air, was considered as mild-moderate COVID-19.[15,16] Severe COVID-19 was defined according to the following criteria: respiratory distress (respiratory rate ≥ 30 breaths/min), severe hypoxemia (oxygen saturation of ≤ 93% at rest or a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen < 300 mmHg) or critical illness.[15–17]

2.4 | Statistical analysis

The data were analyzed using the Biomedical Package software program.[26] The results were expressed as means and standard deviations for quantitative data or as numbers (percentages) for qualitative data. Statistical comparisons were performed between the data obtained for groups 1 vs. 2 and A vs. B. Pearson's chi-square or Fisher's exact test was used for comparison of discrete variables. Analysis of variance (ANOVA) was applied for continuous variables. Survival curves were plotted using the Kaplan-Meier estimate. Differences between the curves were evaluated by the Mantel-Cox test. *P*-values ≤ .05 were considered statistically

significant. Variables that were found to be associated with decreased survival using the univariate analysis were re-evaluated by the Cox proportional-hazards model, to identify those most significantly associated with mortality.

3 | RESULTS

3.1 | Patient characteristics

3.1.1 | Entire sample

The demographic, clinical and laboratory data of the 477 patients included in the study are presented in Table 1. The mean age was 64.0 ± 18.7 years (range 18−100) and 50.3% were males. The most common comorbidities were hypertension, diabetes mellitus and anemia. Fever, cough, dyspnea and weakness were the most common symptoms presenting on admission. On admission, 60.0% of the patients presented with pneumonia and 25.2% with severe COVID-19. Groups 1 (normal RDW) and 2 (high RDW) comprised 69.4% and 30.6% of the patients, respectively.

3.1.2 | Comparisons according to RDW at admission (group 1 vs. 2, Table 1)

Patients with high RDW on admission (group 2) were older and more likely to present with comorbidities than were those with normal RDW on admission (group 1). A higher proportion of patients in group 2 than group 1 complained of dyspnea on admission, and a lower proportion complained of cough, headache, diarrhea and myalgia. Patients from group 2 were more likely to be admitted with severe COVID-19 and lower mean values of diastolic blood

pressure and oxygen saturation. At admission, the mean values of serum albumin and blood hemoglobin and hematocrit were lower, and the mean levels of serum glucose and creatinine were higher, in group 2 than group 1. Treatments including beta-lactam antibiotics, anticoagulants and corticosteroids were more often administered to patients in group 2.

3.1.3 | Comparisons according to RDW changes (group A vs. B, Table 2)

Among 412 patients with available data, RDW remained stable during hospitalization in 63.6% (group A) and changed in 36.4% (group B). Patients with a change in RDW were older and more often presented with hypertension, diabetes mellitus, anemia, renal failure, obesity, coronary artery disease, heart failure and complex nursing care than did those without significant change in RDW.

The mean levels of diastolic blood pressure at admission, and the mean values of oxygen saturation on admission and discharge, were significantly lower in group B than in group A. Moreover, on admission, higher proportions of patients in group B demonstrated pulmonary infiltrates, pleural effusion and severe COVID-19. Compared to patients in group A, patients in group B were more often treated with beta-lactam antibiotics, remdesevir, anticoagulants, corticosteroids, hydroxychloroquine and convalescent plasma.

Regarding laboratory data, higher mean values of creatinine and C-reactive protein (CRP) in serum; and leukocytes, neutrophils and RDW in blood, were observed both at admission and discharge, in group B than in group A. In addition, the mean levels of albumin, hemoglobin and hematocrit were lower during hospitalization in group B. Finally, lymphopenia on admission and discharge more often presented among patients in group B.

3.2 | In-hospital outcomes

3.2.1 | Entire sample

Table 1 presents the outcomes during the current hospitalization. The rate of hospital mortality was 12.6%.

3.2.2 | Comparisons according to RDW at admission (group 1 vs. 2, Table 1)

During the hospitalization, patients in group 2 compared to group 1 more often developed nosocomial infection, were transferred to the intensive care unit and were mechanically ventilated. The mean length of hospital stay was longer and the rate of in-hospital death was significantly higher in group 2 than in group 1 (20.5% vs. 9.1%, $P < .001$).

3.2.3 | Comparisons according to RDW changes (group A vs. B, Table 2)

Throughout the current hospitalization, a higher proportion of patients in group B than group A demonstrated pneumonia, nosocomial infection and venous thromboembolism. Moreover, patients in group B compared to group A were more often transferred to the intensive care unit and treated with mechanical ventilation; the mean hospital stay was longer and the mortality rate was higher: 29.3% vs. 4.2%.

3.3 | Survival

3.3.1 | Univariate analysis

The follow-up period extended up to 217 days (median of 83 days). During this period, 72 patients (15.1%) died. High vs. normal RDW on admission was associated with shortened survival (Figure 2A): the respective mortality rates and mean survival durations were 26.7% and 83.8 days vs. 10.0% and 99.9 days ($P < .001$). A change in RDW compared to stable RDW was also associated with poor survival (Figure 2B). The mortality rates and mean survival durations were 34.7% and 77.8 days vs. 5.7% and 102.2 days, respectively ($P < .001$). Other variables associated with decreased survival in the entire cohort were: advanced age, male sex, hypertension, diabetes mellitus, anemia, renal failure, cerebrovascular disease, obesity, coronary artery disease, heart failure and chronic lung disease.

3.3.2 | Multivariate analysis (Table 3)

The variables most significantly associated with shortened survival on univariate analysis, were re-evaluated for their association with survival by the Cox proportional-hazards model. The latter analysis was performed separately for RDW on admission and on discharge (as continuous variables), and for change in RDW as a dichotomized variable (stable vs. changed). RDW on admission in the entire sample and in the group evaluated for RDW changes during hospitalization was not among the variables that were found to be most significantly associated with survival. However, each 1% increment of RDW at discharge was strongly associated with low survival ($P = .010$, relative risk 1.13 and 95% confidence

interval 1.04−1.23). Moreover, change in RDW was among the variables that were most significantly associated with decreased survival ($P < .001$, relative risk 1.50 and 95% confidence interval 1.29−1.75).

4 | DISCUSSION

To the best of our knowledge, this is the first study to investigate associations of time-dependent RDW changes with clinical characteristics and outcomes among hospitalized patients with COVID-19. The main novelty of this investigation is the association observed of dynamic RDW changes during hospital course with more severe clinical and laboratory characteristics, poor in-hospital outcomes and an increased risk of short-term mortality. Moreover, our findings corroborate studies that reported associations of elevated RDW values at hospital admission with more severe COVID-19[19–22] and higher in-hospital mortality.[23,24]

Most previous studies of patients hospitalized with COVID-19 focused on the clinical significance of single RDW measurements at hospital admission.[19–24] The strength of the present investigation is the detailed evaluation of demographic, clinical and laboratory characteristics, as well as outcomes, that were associated with changes in RDW values during hospitalization, even within the normal range. About one-third of our patients demonstrated significant time-dependent RDW changes, which were associated with older age and a more severe clinical and laboratory profile. Thus, compared to patients with stable RDW, patients with a change in RDW were more likely to present with a number of comorbidities, such as: hypertension, diabetes mellitus, anemia, renal failure, obesity, coronary artery disease and heart failure, and with severe COVID-19. Moreover, at admission and discharge, patients with a change in RDW demonstrated higher values of serum creatinine and CRP, and blood leukocytes and neutrophils; and lower levels of albumin, hemoglobin and hematocrit. Finally,

lymphopenia throughout hospitalization more often presented among patients with changes in RDW than among those with stable RDW. Rapid changes in RDW during hospitalization have been reported among patients in internal medicine wards[10] and with various specific disorders such as acute myocardial infarction,[4] exacerbated heart failure,[7] community-acquired pneumonia,[11] influenza,[12] sepsis[13] and COVID-19.[24] The pathophysiological mechanisms of the rapid change in RDW in COVID-19 are not understood. Severe inflammation caused by SARS-CoV-2 infection and bacterial super-infections is likely the main contributing factor. An excessive release of pro-inflammatory cytokines (such as interleukin-1 and tumor necrosis factor-α) and humoral mediators results in increased destruction of red blood cells and impaired erythropoiesis. Consequently, an accelerated release of larger erythrocytes into the circulation leads to rapid changes in erythrocyte size.[2,21,22] Indeed, a cytokine release syndrome with marked elevation of inflammatory markers has been recognized in severe COVID-19.[17,21] Another possible underlying mechanism is direct erythrocyte injury by SARS-CoV-2 infection in blood and bone marrow.[22] The aforementioned explanations are supported by our finding of an association of change in RDW with alterations in inflammatory biomarkers such as CRP, albumin and neutrophils, and with the development of nosocomial infection and anemia during hospitalization.

Interestingly, we observed that patients with a change in RDW were more often treated with beta-lactam antibiotics, remdesevir, anticoagulants, corticosteroids, hydroxychloroquine and convalescent plasma than were those with stable RDW. This probably reflects a more severe clinical course of COVID-19. An additional important finding is the demonstration of prognostic significance of changes in RDW values during hospitalization. Association of rapid time-dependent RDW changes with poor outcomes were reported among a heterogeneous population of internal medicine patients,10 and among patients with specific

cardiovascular[4,7] and infectious [11–13] disorders. In their study of 1641 patients with COVID-19, Foy et al. found an association of increased RDW during hospitalization with higher risk of in-hospital mortality.[24] Our findings are in concordance with the results of that study. However, we also found associations of changes in RDW with additional poor in-hospital outcomes such as: pneumonia, nosocomial infection, venous thromboembolism, transfer to the intensive care unit, treatment with mechanical ventilation and prolonged hospital stay. Moreover, a change in RWD appeared as one of the variables (in addition to advanced age, male gender and renal failure) that were most significantly associated with decreased short-term survival.

Underlying mechanisms between the dynamic RDW changes and poor outcomes in hospitalized COVID-19 patients are unclear. Possible explanations include inflammation, oxidative stress and organ dysfunction. Change in RDW in COVID-19 may be a marker of a more severe inflammatory status, which may confer increased risks of severe illness and mortality.[21,22] Additionally, changes in RDW values may be related to severe oxidative stress associated with COVID-19 pneumonia and certain comorbid conditions, thus leading to poor outcomes.[2,11,22] Finally, RDW may change in hospitalized patients with COVID-19 due to dysfunction of various organs, such as the kidney, liver and heart, resulting in worse outcomes.[13,21]

In the present investigation, 30.6% of hospitalized patients with COVID-19 demonstrated high RDW levels at admission. We provided detailed demographic, clinical and laboratory characteristics associated with high baseline RDW. Patients with high RDW on admission were older and presented with a more severe clinical and laboratory profile than did those with normal RDW. Our data corroborate other studies of patients with COVID-19 that reported an association of elevated RDW values on hospital admission with more severe COVID-19.[19–22] The proportion of our patients with elevated RDW at admission was similar

to that reported by Foy et al.,[24] while lower than the 49.7% reported among 294 patients hospitalized with COVID-19 by Ramachandran et al.[23] This discrepancy may be explained by the more severe baseline characteristics in the entire population of the latter study. Indeed, our patients were less likely to complain of cough and dyspnea, or to present with hypertension, diabetes mellitus, renal failure, anemia, lymphopenia and pneumonia. Thus, our lower rate of in-hospital mortality is unsurprising (12.6% vs. 19.0%). Our finding of an association of increased RDW at admission with an increased risk of in-hospital mortality confirms previously reported data.[23,24] In our evaluation of additional outcomes, we observed associations of high RDW at admission with nosocomial infection, transfer to the intensive care unit, treatment with mechanical ventilation, prolonged hospital stay and decreased short-term survival. However, in multivariate analysis, a higher RDW value at admission did not remain one of the variables most significantly associated with shortened survival. Therefore, we suggest that, in our patient population, high baseline RDW serves as a non-specific marker of the severity of COVID-19 and associated morbid conditions, rather than as a predictor of mortality.

The present investigation has a number of limitations. First, as a single center study, the results may not be generalizable to other medical centers. Second, the study was retrospective. In this design, laboratory tests were performed according to the discretion of the treating physician rather than research considerations. Therefore, patients without available measurements of RDW at discharge were excluded from the analysis of time-dependent RDW changes. Moreover, the results may be affected by missing data that is typical of retrospective studies. Third, changes in the protocol for treatment of COVID-19 during the study period may have affected the outcomes.

5 | Conclusion

Both high RDW values at admission and rapid changes in RDW levels are common among patients hospitalized with COVID-19, and are associated with a severe clinical profile and poor in-hospital outcomes. Moreover, change in RDW during hospitalization is strongly associated with an increased risk of short-term mortality. RDW determination is routine, simple and inexpensive. We suggest that repeated evaluation of RDW may provide useful information for the improvement of care of patients hospitalized with COVID-19.

DISCLOSURE

The authors declare no potential conflicts of interest with respect to authorship, and/or publication of this study.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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LEGENDS TO FIGURES

FIGURE 1 Flowchart presenting the study design.

COVID-19, coronavirus disease 2019; CBC, complete blood count; RDW, red cell distribution width; ΔRDW, RDW on discharge minus RDW on admission.

FIGURE 2 The Kaplan-Meier estimates of survival for the various study groups.

(A) Association between RDW on admission and survival. Group 1: normal (≤ 14.7%) RDW on admission. Group 2: high RDW (> 14.7%) on admission.

(B) Association between ΔRDW (RDW on discharge minus RDW on admission) and survival. Group A: no significant change in RDW (ΔRDW up to ± 0.4%). Group B: significant change in RDW (ΔRDW > ± 0.4%).

RDW, red cell distribution width.