LETTER TO THE EDITOR

Red cell distribution width is associated with mortality in non-anemic patients with COVID-19

To the Editor,

We have read with great interest the meta-analysis that examined the impact of increased red cell distribution width (RDW) and coronavirus disease 2019 (COVID-19) outcomes, conducted by Lee and colleagues, and recently published in the Journal of Medical Virology. The authors concluded that elevations in RDW were associated with adverse COVID-19 outcomes.[1] However, as a large subset of hospitalized COVID-19 patients are anemic (over 30% in our own study),[2] the impact of elevation of RDW independent of anemia in COVID-19 remains to be clarified.[1,3,4] Here we have analyzed a large population of COVID-19 patients and addressed whether the impact of RDW on mortality in this cohort is related to their anemia.

Patients ≥18 years who were diagnosed with COVID-19 at the Mount Sinai Health System between March 1 and April 1, 2020 and had a complete blood count at presentation (n = 2562) were selected to assess the association between RDW and mortality. Anemia was defined by WHO criteria (hemoglobin levels <13 g/dL for males and less than 12 g/dl for females) and an elevated RDW was defined as greater than 15%. Comorbidities were assessed using the Charlson comorbidity index (CCI). As patients did not have uniform follow up time, multivariable Cox proportional hazards regression models, stratified by presence of anemia, were performed to assess the association of RDW with mechanical ventilation and mortality independent of the effects of age, sex, race, and CCI. All analyses were performed using SAS software, v9.4 (SAS Institute). This study was approved by the Program for Protection of Human Subjects of the Icahn School of Medicine at Mount Sinai.

Among 2562 patients with COVID-19 for whom complete blood count was obtained, 501 patients (19.6%) had an elevated RDW at the time of diagnosis (Table 1). At univariate analysis, elevated RDW was statistically significantly associated with mechanical ventilation (p = .0109) and mortality (p < .0001). We found that elevated RDW was statistically significantly associated with higher risk of both being placed on a ventilator (adjusted hazards ratio [HR$_{adj}$]: 1.66, 95% confidence interval [CI]: 1.19–2.32) and mortality (HR$_{adj}$: 1.60, 95% CI: 1.18–2.15)in non-anemic patients, but there was no association in anemic patients (Table 2). These associations were independent of the effects of age, sex, race, and CCI. There was a statistically significant interaction between anemia and RDW when the associations with mechanical ventilation (p = .02) and mortality (p = .01) were studied.

Previous studies have found that elevations in RDW are predictive of mortality in numerous settings,[5,6] as it may serve as an early indicator of physiological stress via reductions in erythropoietic output.[7] To address the value of RDW elevations in the context of anemia, in this study of a large sample of COVID-19 patients, unlike the previously referenced studies,[1,3,4] we stratified our large sample of patients according to their hemoglobin levels and included patients that were not hospitalized. We confirmed that RDW elevation is independently predictive of morbidity and mortality in COVID-19. In addition, for the first time we show that the elevated RDW association with mortality and mechanical ventilation is present exclusively in non-anemic patients. The underlying mechanism implicated in this association is speculative. Considering the tight association of elevated RDW with anemia and the fact that anemia is an independent predictor of disease severity, the predictive value of RDW may not surpass that of anemia and only be exposed in non-anemic patients. Therefore, we propose that RDW be considered by clinicians, especially in non-anemic patients, when risk-stratifying COVID-19 patients.

CONFLICT OF INTERESTS

The authors delcare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Rapp, Tremblay, Mascarenhas, Taioli, Ghaffari. Acquisition, analysis, or interpretation of data, drafting of the manuscript, Critical revision of the manuscript for

TABLE 1 Baseline characteristics of patients (N = 2562)

Variable	N (%)
Sex	
Male	1458 (56.9)
Female	1104 (43.1)
Race	
Non-Hispanic white	632 (24.7)
Hispanic and/or nonwhite	1930 (75.3)
Age (years)	
<52	628 (24.5)
52–63	605 (23.6)
64–75	707 (27.6)
>75	622 (24.3)
Red blood cell distribution width (%)	
>15	501 (19.6)
≤15	2061 (80.4)
Anemia (hemoglobin < 12 g/dl, females; <13 g/dl, males)	
Yes	792 (30.9)
No	1770 (69.1)
Variable	Mean (SD)
Charlson comorbidity index	1.71 (2.09)

TABLE 2 Predictors of being placed on mechanical ventilation and mortality among COVID-19 positive patients according to anemia status

	Non-anemic patients (n = 1770)	
Variable	Mechanical ventilation HR$_{adj}$[a] (95% CI)	Mortality HR$_{adj}$[a] (95% CI)
RDW (%) >15 versus ≤15	1.66 (1.19–2.32)	1.60 (1.18–2.15)
Female versus male	0.65 (0.52–0.82)	0.69 (0.55–0.85)
Non-Hispanic white versus Hispanic and/or nonwhite	0.73 (0.56–0.95)	0.90 (0.71–1.14)
Age (years)		
<52	1.0 (Ref)	1.0 (Ref)
≥52–63	1.91 (1.39–2.67)	1.93 (1.25–2.98)
64–75	2.46 (1.77–3.42)	3.42 (2.29–5.13)
>75	1.81 (1.23–2.65)	6.63 (4.41–9.96)
Charlson comorbidity index	0.97 (0.91–1.04)	1.03 (0.98–1.09)
Anemic patients (n = 792)		
RDW (%) >15 versus ≤15	0.91 (0.66–1.25)	0.96 (0.74–1.25)
Female versus male	0.99 (0.72–1.36)	0.76 (0.58–0.99)
Non-Hispanic white versus Hispanic and/or nonwhite	1.08 (0.76–1.54)	1.23 (0.94–1.62)
Age (years)		
<52	1.0 (Ref)	1.0 (Ref)
≥ 52–63	1.37 (0.76–2.46)	4.94 (2.22–11.03)
64–75	2.31 (1.37–3.91)	6.88 (3.17–14.97)
>75	1.48 (0.86–2.57)	10.10 (4.67–21.76)
Charlson comorbidity index	1.02 (0.95–1.09)	1.07 (1.01–1.12)

Note: The High RDW*Anemia interaction term was statistically significant for both mechanical ventilation (p = .02) and mortality (p = .01).

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HRadj, adjusted odds ratio; RDW, red cell distribution width; Ref, reference.

[a]Adjusted for all variables listed.

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