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LETTER TO THE EDITOR

Monocyte distribution width adds prognostic value in detection of COVID-19 respiratory failure

Dear Editors,

The coronavirus disease 2019 (COVID-19) pandemic has stressed the resource-limited healthcare systems to a breaking point.[1,2] In light of limited intensive care unit bed capacity, the ability to determine that patients require a higher level of care for COVID-19 induced hypoxemic respiratory failure (RF) is critical.[3] Several risk scoring systems have been proposed as a result.[4,5] Many rely on routinely obtained laboratory data from cell count and population analyzers, with neutrophil-to-lymphocyte ratio (NLR) emerging as a leading predictor of COVID-19 disease severity.[6] The monocyte distribution width (MDW), another potential product of cell count analyzers, has been shown to be a reliable early marker of sepsis.[7] While MDW is also elevated in patients with severe COVID-19, it is not clear if the measure adds any prognostic value beyond the more routinely available NLR.[8]

We leveraged retrospective data to assess the additive value of MDW to NLR in predicting the risk of hypoxemic RF in patients with COVID-19 presenting to the emergency department (ED) setting at an academic safety-net healthcare system in Northeast Ohio. The patient cohort comprised those who visited the ED with a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR between 7 days prior to and 5 days after arrival, between May 1, 2020 and February 8, 2021. We excluded patients who arrived as trauma activations, had a charted history of hematologic malignancies and myelodysplastic syndromes, lacked cell count differential data, or had these tests drawn after developing the primary outcome (RF). Hypoxemic RF was defined as the need for mechanical ventilation, high-flow nasal cannula, or non-rebreather, venturi, or simple face mask during the encounter. For each encounter, we collected demographic data, vital signs, and laboratory data. The latter included blood cell count differential data and the MDW measure as reported by the Beckman Coulter DxH 900 analyzer.

Monocyte distribution width and NLR discrimination for hypoxemic RF was computed using area under the curve measures with 95% confidence intervals. Optimal specificity and sensitivity cutoffs for each biomarker were determined using Youden's index. Logistic regressions were developed to predict RF using NLR alone, and then NLR with the addition of MDW. The additive value of MDW to NLR was determined using a likelihood ratio chi-squared test, and the fraction of new information added to the NLR-only model by MDW determined using Harrell's approach.[9] Finally, a Kaplan-Meier curve was constructed to show the value of combining MDW and NLR assessments at our proposed cutoffs on predicting RF. Institutional review board approval was ascertained prior to the initiation of this study. No funding was received for this study.

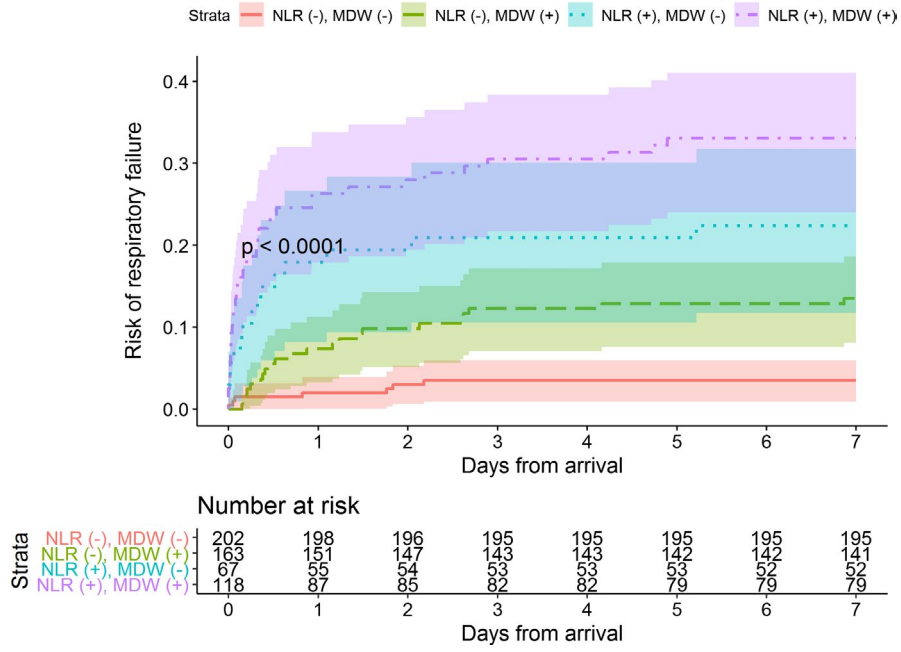

FIGURE 1 Time to hypoxemic respiratory failure (RF) from arrival, stratified by monocyte distribution width (MDW) and neutrophil-to-lymphocyte ratio (NLR) above and below our established thresholds. There were 118 patients in the NLR+, MDW + group; 67 patients in the NLR+, MDW- group; 163 patients in the NLR-, MDW + group; and 202 patients in the NLR-, MDW- group. For this figure and accompanying analysis, the outcome was censored at 7 d. Patients who did not develop RF and were discharged alive were assumed not to meet criteria for RF on day 7. NLR (+) = NLR ≥5.46, MDW (+) = MDW ≥23.5. $P < .0001$ by log-rank test

TABLE 1 Results of a logistic regression for risk of respiratory failure

	NLR alone		NLR + MDW	
Variables[†]	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
NLR	1.90 (1.44-2.52)	<.001	2.18 (1.55-3.07)	<.001
MDW			1.70 (1.30-2.22)	<.001
NLR × MDW (interaction term)			0.74 (0.61-0.92)	<.01
Model performance				
Chi-square	26.74		47.37*	

Abbreviations: CI, Confidence interval; MDW, Monocyte distribution width; NLR, Neutrophil to lymphocyte ratio; OR, Odds ratio.

[†]MDW and NLR have been scaled according to value mean and standard deviation.

*$P < .001$ compared to NLR alone.

There were a total 2429 encounters with patients who met inclusion criteria. 1879 were excluded. Exclusions included 58 with patients who had a history of hematologic malignancy or myelodysplastic syndromes, 41 encounters that arrived as trauma activations, 1734 that lacked cell count differential data, 35 encounters representing patients with repeat encounters, and 11 encounters where hypoxemic RF preceded the blood draw. The final cohort consisted of 550 patients. The average age was 57.6 years ± 15.9 (SD). In our cohort, 280 (50.9%) were female, 204 (37.1) were White, and 261 (47.5%) were Black. Of the 550 patients included in the study, 318 (57.8%) were admitted to the inpatient setting, 83 (15.1%) had an outcome of RF, while 79 (14.4%) had an outcome of death or 3-day ICU admission.

The median MDW and NLR in encounters with RF were 26.0 (interquartile range [IQR]: 23.0-28.0) and 7.08 (IQR: 4.32-10.67), respectively. The median MDW and NLR in encounters without RF were 23.0 (IQR: 21.0-26.0) and 3.48 (IQR: 1.98-6.27), respectively. The c-statistic (equivalent to area under the receiver operator curve) was 0.73 (95% CI: 0.67-0.78) for NLR and 0.68 (95% CI: 0.62-0.74) for MDW. The Youden's index cutoff for NLR was 5.46 (66% sensitivity, 72% specificity), and for MDW was 23.5 (74% sensitivity, 53% specificity).

The results of univariate analysis of NLR and the multivariate analysis of NLR in addition to the MDW are shown in Table 1. The likelihood ratio chi-squared (LR χ^2) test comparing these two models demonstrated that the combined NLR plus MDW model was statistically significantly better at predicting hypoxemic failure than NLR alone (LR $\chi^2 = 20.6$, $P < .001$). The adequacy index calculated from the likelihood ratio chi-squared was 0.56; thus, the fraction of new information from the addition of MDW to NLR was 43.5%.[9]

When NLR and MDW were both below their individual Youden's index cutoffs, the negative predictive value for respiratory failure was 96.5%. To further illustrate the value of both measures, a time to event analysis for patients stratified by our derived NLR and MDW threshold values is presented in Figure 1.

Although prior studies have separately evaluated MDW and NLR as biomarkers for COVID-19 prognostication, ours is the first to evaluate the value of both biomarkers together.[6,10] The immune response to severe COVID-19 is associated with dysregulated expression of IL-7 and IL-10, as well as increased neutrophil conductivity thought be reflected in elevations of both the NLR and MDW.[8] While the MDW measure is Food and Drug Administration approved as an early sepsis indicator in adults presenting to the ED setting, its use is not ubiquitous. Our results suggest that when available, MDW can add useful prognostic information with regards to the ability to predict hypoxemic RF early in a patient's course. The strengths of our study include a relatively large and diverse patient sample size and the inclusion of most patients presenting to the ED with a routinely obtained cell count differential. Limitations include reliance on a single-center experience and the lack of external validation. Even though our test characteristics and chosen thresholds may not be generalizable, our results nonetheless strengthen the case for MDW as an important, independent predictor of decompensation in the context of COVID-19. Future work on COVID-19-specific risk stratification scoring systems or models should consider inclusion of this measure in addition to more widely available cell population parameters.

KEYWORDS

Coronavirus, COVID-19, monocyte distribution width, neutrophil-to-lymphocyte ratio, respiratory failure

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CONFLICT OF INTEREST

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Yasir Tarabichi, upon reasonable request.

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