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Hematological ratios as an alternative to D-dimers for predicting COVID-19-related mortality in a resource-limited setting

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ABSTRACT

Introduction
The COVID-19 pandemic has highlighted the critical role of biological biomarkers in the prognostic assessment of hospitalized patients. D-dimers are among the most reliable prognostic biomarkers in COVID-19; however, their measurement may be difficult to access in resource-limited healthcare settings. Hematological ratios derived from the complete blood count—particularly the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR)—have been proposed as simple and cost-effective alternatives.

Purpose
To compare the prognostic value of hematological ratios (NLR, PLR, and LMR) with that of D-dimers for predicting COVID-19–related mortality in a resource-limited setting.

Methods
We conducted a retrospective cross-sectional study including patients hospitalized for COVID-19 at the Military Hospital of Camp Kokolo in Kinshasa (Democratic Republic of the Congo) between May 2020 and August 2021. A total of 480 hospitalized patients were included, among whom 76 deaths were recorded. Biological biomarkers measured at admission included D-dimers and the NLR, PLR, and LMR ratios. Discriminatory performance for mortality prediction was assessed using receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC) and 95% confidence intervals (CIs).

Results
D-dimers demonstrated excellent prognostic performance (AUC = 0.91; 95% CI [0.88, 0.94]). In contrast, hematological ratios showed limited discriminatory ability: NLR (AUC = 0.58; 95% CI [0.43, 0.74]), PLR (AUC = 0.39; 95% CI [0.20, 0.59]), and LMR (AUC = 0.52; 95% CI [0.33, 0.72]).

Conclusion
In this cohort, D-dimers were markedly superior to hematological ratios for predicting COVID-19–related mortality. Although readily accessible, NLR, PLR, and LMR demonstrated limited prognostic utility when used in isolation in resource-limited settings.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, China, before rapidly spreading worldwide and leading to a major global pandemic (Huang et al., 2020; Zhu et al., 2020). Although infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily presents with respiratory symptoms, it is now well established that COVID-19 is a systemic disease capable of affecting multiple organs and systems, including the hematological system (Attaway et al., 2021; Mao et al., 2020).

Several studies have demonstrated that SARS-CoV-2 infection is associated with significant hematological abnormalities, including lymphopenia, neutrophilia, alterations in platelet count, and coagulation disorders (Palladino, 2021). These abnormalities are often correlated with disease severity and mortality risk, underscoring the critical role of biological parameters in the prognostic assessment of patients with COVID-19 (Pourbagheri-Sigaroodi et al., 2020).

Among the investigated biomarkers, D-dimers are considered one of the most reliable indicators of coagulation activation and poor prognosis in patients with COVID-19 (Nemec et al., 2022). Elevated D-dimer levels reflect excessive activation of the fibrinolytic system and have been associated with an increased risk of thromboembolic complications and mortality (Merdji et al., 2021). However, D-dimer testing requires specialized laboratory equipment that is not always available in resource-limited healthcare settings.

In many low- and middle-income countries, access to specialized laboratory testing remains limited due to shortages of equipment, reagents, and laboratory infrastructure. This constraint restricts the routine use of certain prognostic biomarkers, particularly D-dimers, in the management of patients with COVID-19 (Chapanduka et al., 2022; Moueden & Seghier, 2021). Despite the substantial impact of the pandemic in these settings, scientific data on the use of simple and accessible prognostic biomarkers remain insufficient.

In this context, hematological ratios derived from the complete blood count (CBC), such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have attracted increasing interest as potentially useful inflammatory markers for assessing COVID-19 severity (Delshad et al., 2021; Liu et al., 2020).

The neutrophil-to-lymphocyte ratio is a well-established indicator of systemic inflammation. Several studies have shown that an elevated NLR is associated with worse clinical outcomes and increased mortality among patients hospitalized with COVID-19 (Li et al., 2020; Liu et al., 2020). This elevation reflects an immune imbalance characterized by enhanced neutrophil-driven inflammatory responses and impaired lymphocyte-mediated immunity.

The lymphocyte-to-monocyte ratio has also been proposed as a useful inflammatory biomarker for assessing disease severity. A low LMR at hospital admission has been associated with faster progression of pneumonia and poorer prognosis in patients infected with SARS-CoV-2 (Koval et al., 2021).

Similarly, the platelet-to-lymphocyte ratio is considered a composite marker of inflammation and platelet activation. Several studies have suggested that an elevated PLR may be associated with increased clinical severity and mortality in patients with COVID-19 (Sarkar et al., 2022). However, findings remain inconsistent, and the prognostic value of this biomarker continues to be debated in the scientific literature (Simon et al., 2022).

The main advantage of these hematological ratios lies in their derivation from the CBC, a simple, inexpensive, and widely available test, including in resource-limited healthcare settings. As such, they may represent valuable alternatives to more costly or less accessible biomarkers, such as D-dimers, for the prognostic evaluation of patients with COVID-19.

Therefore, the present study aimed to compare the prognostic value of the hematological ratios NLR, LMR, and PLR with that of D-dimers, which are considered a reference biomarker for assessing the risk of disease severity and mortality in patients infected with SARS-CoV-2. The objective was to determine the extent to which these simple hematological indices may serve as useful

tools for guiding clinical management in resource-limited settings.

METHODS

Study Design and Setting

This was a retrospective cross-sectional study based on data collected from patients hospitalized for COVID-19 at the Military Hospital of Camp Kokolo in Kinshasa, Democratic Republic of the Congo.

Study Population

The study population consisted of patients admitted with a diagnosis of COVID-19 at the Military Hospital of Camp Kokolo between May 2020 and August 2021. The total sample size was 480 patients, among whom 76 deaths were recorded during hospitalization.

A patient was considered to have COVID-19 if the following criteria were met:

- Presence of signs and symptoms suggestive of COVID-19 according to the clinical case definition;
- Laboratory confirmation of infection by detection of SARS-CoV-2 or its components using reverse transcription polymerase chain reaction (RT-PCR) or a rapid antigen test.

Inclusion Criteria

The following patients were included:

- Patients hospitalized at the Military Hospital of Camp Kokolo during the study period;
- Patients with a confirmed diagnosis of COVID-19;
- Patients with at least one complete blood count and D-dimer measurement available in their medical records.

Exclusion Criteria

The following patients were excluded:

- Patients with incomplete medical records for the biological parameters of interest;
- Patients lacking usable results for the studied biomarkers;
- Observations with noninterpretable values for hematological ratios (e.g., division by zero).

Data Collection

Data were retrospectively extracted from the medical records of hospitalized patients. The collected information included:

- Demographic characteristics (age and sex);
- Medical history;
- Biological parameters.

Peripheral blood count parameters included:

- Total white blood cell count;
- Absolute neutrophil count;
- Absolute lymphocyte count;
- Absolute monocyte count;
- Platelet count.

Coagulation parameters included:

- Fibrinogen;
- D-dimers.

Blood samples used for biological analyses were collected within the first 24 hours of hospitalization.
The hematological ratios were calculated as follows:

- **Neutrophil-to-lymphocyte ratio (NLR):** absolute neutrophil count divided by absolute lymphocyte count;
- **Platelet-to-lymphocyte ratio (PLR):** platelet count divided by absolute lymphocyte count;
- **Lymphocyte-to-monocyte ratio (LMR):** absolute lymphocyte count divided by absolute monocyte count.

Clinical outcomes (survival or death) were collected and used as the primary endpoint. To ensure confidentiality, all data were anonymized prior to analysis.

Statistical Analysis

Data were entered and analyzed using IBM SPSS Statistics (Version 25; IBM Corp., Armonk, NY, USA). Quantitative variables were assessed for normality using graphical inspection (histograms) and, when necessary, formal normality tests. Due to the skewed distribution observed for most biological parameters, nonparametric methods were applied.

Quantitative variables were described using the median and interquartile range (IQR), whereas qualitative

variables were presented as frequencies and percentages. Patients were divided into two groups based on clinical outcome:

- Survivors;
- Non-survivors.

Comparisons of biological biomarkers (D-dimers, NLR, PLR, and LMR) between the two groups were performed using the Mann–Whitney U test due to non-normal distributions and the frequent presence of extreme values in biological data from COVID-19 patients.

The prognostic performance of biomarkers for predicting mortality was evaluated using receiver operating during the calculation of hematological ratios were excluded.

To identify biomarkers independently associated with mortality, a multivariable logistic regression analysis was performed, adjusting for age and sex. All statistical analyses were two-sided, with a significance level set at $p < .05$.

Ethical Considerations

This study was conducted in accordance with the ethical principles of biomedical research and patient data confidentiality. The study protocol was approved by the Ethics Committee of the School of Public Health, Faculty of Medicine, University of Kinshasa (approval letter No. ESP/CE/12B/2024 dated February 2, 2024).

characteristic (ROC) curve analysis. For each biomarker, the area under the curve (AUC) was calculated along with its 95% confidence interval (CI), when applicable.

AUC values were interpreted according to conventional thresholds:

- AUC = 0.50: no discrimination;
- AUC = 0.60–0.70: poor to fair discrimination;
- AUC = 0.70–0.80: good discrimination;
- AUC > 0.80: excellent discriminatory ability.

ROC analyses were performed only on observations with complete data for the studied biomarkers. Infinite or noninterpretable values resulting from division by zero

RESULTS

During data collection, 508 patient records were reviewed. Of these, 21 were excluded due to missing complete blood count results. Ultimately, 487 patients were eligible for inclusion. However, because clinical outcome data were unavailable for 7 patients, the final analysis included 480 patients. Among them, 404 (84.17%) were survivors (recovered), while 76 (15.83%) were non-survivors (deceased).

General Characteristics of Patients

Table 1 presents the general characteristics of patients according to clinical outcome.

Table 1:
General characteristics of patients according to clinical outcome

Parameter	N	Total	Survivors (n = 404)	Non-survivors (n = 76)	*p* value	Crude OR	*p* value	Adjusted ORa	*p* value
Sex	480				< .001				
Male	406	406 (100%)	352 (87%)	54 (13%)		Ref		Ref	
Female	74	74 (100%)	52 (70%)	22 (30%)		2.76	< .001	1.48	.341
Age (years)	480	29 (25–58.5)	27 (25–47)	69 (54.75–79.25)	< .001	1.08	< .001	1.07	< .001
D-dimers (ng/mL)	430	253 (248–508)	252 (246.25–450)	635 (518.75–893.03)	< .001	1.003	< .001	1.001	.031

Note: Values are *n* (%) or median (IQR). Ref = reference category. OR = odds ratio. IQR = interquartile range. D-dimer measurements were available for 430 patients; percentages for D-dimers are calculated using available-case analysis.

Adjusted odds ratios were obtained from multivariable logistic regression adjusted for age and sex.

Age and D-dimer levels were significantly higher ($p < .001$) among non-survivors (median age: 69 years; median D-dimers: 635 ng/mL) than among survivors (median age: 27 years; median D-dimers: 252 ng/mL), suggesting an association between advanced age, coagulation activation, and COVID-19-related mortality in this setting.

Although the proportion of deaths was higher among females (22/74; 30%) than males (54/406; 13%) ($p < .001$),

this association did not remain statistically significant after multivariable adjustment (Table 1).

Overall, although crude mortality appeared higher among females, the study population was predominantly male (406/480; 84.6%; male-to-female ratio ≈ 5.5:1) and relatively young (approximately three-quarters were younger than 60 years). In addition, 93/480 (19.38%) had comorbidities.

Comparison of Hematological Ratios

Hematological ratios derived from the complete blood count were compared between survivors and non-survivors.

Table 2:
Comparison of hematological ratios between survivors and non-survivors

Ratio	Survivors (median)	Non-survivors (median)	*p* value
NLR	1.71	1.65	.302
PLR	79.74	53.92	.265
LMR	17.5	38.0	.187

Note: NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; LMR = lymphocyte-to-monocyte ratio.

No statistically significant differences were observed for NLR, PLR, or LMR between survivors and non-survivors ($p > .05$).

Prognostic Performance of Biomarkers (ROC Analysis)

The discriminatory ability of biomarkers for predicting mortality was evaluated using receiver operating characteristic (ROC) curve analysis.

Table 3:
Prognostic performance of biomarkers for predicting mortality

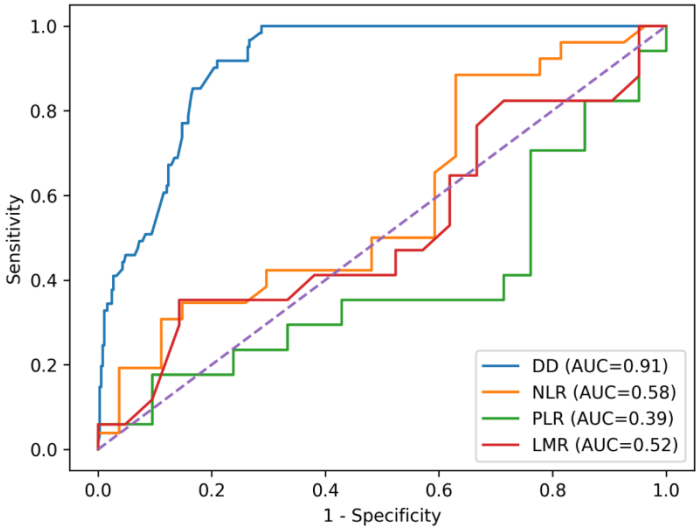
Biomarker	AUC	95% CI	Interpretation
D-dimers	0.91	[0.88, 0.94]	Excellent
NLR	0.58	[0.43, 0.74]	Poor
PLR	0.39	[0.20, 0.59]	No discrimination
LMR	0.52	[0.33, 0.72]	No discrimination

D-dimers demonstrated the highest discriminatory ability for predicting mortality, with an AUC of 0.91 (95% CI [0.88, 0.94]), indicating excellent prognostic performance.

In contrast, hematological ratios showed limited performance. NLR demonstrated very limited discriminatory ability (AUC = 0.58; 95% CI [0.43, 0.74]), while PLR and LMR showed no meaningful discriminatory capacity for mortality prediction.

The corresponding ROC curves are presented in Figure 1.

Figure 1:
ROC curves comparing the prognostic performance of D-dimers and hematological ratios (NLR, PLR, and LMR) for predicting mortality among patients hospitalized with COVID-19 at the Military Hospital of Camp Kokolo



DISCUSSION

In this study conducted in a resource-limited setting, we evaluated the prognostic value of hematological ratios derived from the complete blood count (NLR, PLR, and LMR) in comparison with D-dimers for predicting COVID-19–related mortality.

Our findings demonstrate that D-dimers showed the strongest prognostic performance, with an area under the curve (AUC) of 0.91, indicating excellent discriminatory ability. In contrast, hematological ratios showed markedly lower performance, with AUCs of 0.58 for NLR, 0.39 for PLR, and 0.52 for LMR, suggesting poor or negligible discriminatory capacity for mortality prediction in our cohort.

These results indicate that, in our population, hematological ratios derived from routine blood counts cannot substitute for coagulation markers such as D-dimers for prognostic stratification of patients with COVID-19. Our findings therefore reinforce the central role of D-dimers as a major prognostic biomarker in COVID-19.

Several studies have shown that elevated D-dimer levels reflect activation of the coagulation cascade and the formation of microthrombi, phenomena frequently observed in severe forms of the disease (Merdji et al., 2021;

Nemec et al., 2022). The excellent AUC observed in our study is consistent with findings from multiple international cohorts, in which D-dimers have emerged as one of the most robust biological predictors of COVID-19–related mortality (Tang et al., 2020).

In the African context, some studies have also highlighted the importance of coagulation markers. In South Africa, Chapanduka et al. (2022) demonstrated that D-dimers were strongly associated with mortality among hospitalized patients with COVID-19, with superior prognostic performance compared to inflammatory markers derived from complete blood counts. These findings are consistent with our results and suggest that coagulation abnormalities play a key role in adverse outcomes.

Regarding hematological ratios, our results indicate limited prognostic performance of NLR (AUC = 0.58). Although NLR is commonly considered a marker of systemic inflammation, its discriminatory power for predicting mortality was weak in our population. This observation is consistent with findings reported in Ethiopia by Tufa et al. (2021), who also observed limited prognostic value of NLR for COVID-19 mortality, despite a tendency toward higher values in severe cases.

However, several studies conducted in other regions have reported contrasting results. In China, Liu et al. (2020) found that NLR was an independent predictor of mortality in patients with COVID-19, with substantially higher discriminatory performance than observed in our study. Similarly, a meta-analysis by Li et al. (2020) concluded that NLR generally demonstrates good performance for predicting COVID-19 severity and mortality.

These discrepancies may be explained by several factors. First, demographic characteristics differed considerably across study populations. In our study, the median age of non-survivors was significantly higher than that of survivors, confirming that age is a major confounding factor in prognostic analyses. Advanced age is strongly associated with immune dysregulation and an increased risk of thrombo-inflammatory complications (Zhou et al., 2020). Therefore, part of the observed association between biomarkers and mortality may be mediated by age.

Second, the magnitude of the observed effects for hematological ratios was relatively small. Median differences between survivors and non-survivors for NLR, PLR, and LMR were modest and not statistically significant, which is reflected in AUC values close to random. This highlights the importance of considering not only the direction of associations but also their effect sizes. PLR showed particularly poor performance in our study (AUC = 0.39), indicating no discriminatory ability. This finding contrasts with some studies reporting an association between elevated PLR and adverse outcomes in COVID-19 (Sarkar et al., 2022). However, other studies have also demonstrated limited prognostic value of PLR when used in isolation, likely due to variability in platelet counts and the influence of anticoagulant therapies (Simon et al., 2022).

Similarly, LMR demonstrated near-random discriminatory performance in our study (AUC = 0.52). Several observational studies have also reported that, although LMR is of pathophysiological interest, it is not a reliable standalone predictor of mortality (Koval et al., 2021).

Several methodological limitations should be acknowledged. First, the absence of a comprehensive multivariable model incorporating a broader range of clinical and biological variables limited our ability to assess the independent effects of the studied biomarkers. Although some analyses were adjusted for age and sex, other potential confounders, such as comorbidities and baseline clinical severity, were not included in a fully adjusted model.

Second, the retrospective design and the lack of strict standardization in the timing of biological sample collection may have influenced the results. The temporal dynamics of inflammatory and coagulation markers during disease progression can affect their prognostic value.

Finally, the sample size and number of events may have reduced the precision of statistical estimates, particularly for ROC analyses.

Despite these limitations, this study provides original data from an African resource-limited setting, where evidence

regarding prognostic biomarkers in COVID-19 remains scarce.

Overall, our findings suggest that D-dimers remain substantially superior to hematological ratios for predicting COVID-19–related mortality. Although NLR, PLR, and LMR are inexpensive and readily available, their prognostic utility appears limited when used in isolation. Nevertheless, their accessibility may support a complementary role in initial risk assessment, particularly in settings where coagulation testing is not available.

Study Limitations

This study has several limitations, including its retrospective and single-center design, which may limit the generalizability of the findings. The incomplete availability of certain biological data—particularly those required for calculating hematological ratios—combined with the lack of strict standardization in sampling time, may have reduced statistical power and underestimated the prognostic value of these biomarkers. Additionally, the absence of multivariable analyses incorporating dynamic clinical and biological parameters limited assessment of the independent effect of each ratio.

CONCLUSION

This study evaluated the prognostic value of hematological ratios derived from the complete blood count—namely the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR)—in comparison with D-dimers for predicting COVID-19–related mortality in a resource-limited setting.

D-dimers demonstrated excellent discriminatory ability for mortality prediction (AUC = 0.91), confirming their central role as a prognostic biomarker in COVID-19, consistent with previous reports (Merdji et al., 2021; Tang et al., 2020). In contrast, the hematological ratios evaluated showed weak or near-random discriminatory performance, with AUC values of 0.58 for NLR, 0.39 for PLR, and 0.52 for LMR, and no significant differences between survivors and non-survivors. These findings do not support the use of these ratios as reliable substitutes for D-dimers in mortality prediction in this population.

These results should be interpreted with caution. The retrospective design limited control of potential confounding factors. In addition, the modest sample size and number of events may have reduced the precision of estimates, particularly in ROC analyses. Furthermore, the lack of a comprehensive multivariable adjustment incorporating additional clinical and biological variables limited assessment of the independent effects of the studied biomarkers. Age, which was significantly higher among non-survivors, represents an important confounder that may influence associations between biomarkers and mortality (Zhou et al., 2020).

Prospective multicenter studies with larger sample sizes, standardized timing of biological sampling, and comprehensive multivariable models incorporating age, comorbidities, and clinical severity indicators are needed to better define the potential role of hematological ratios within combined prognostic models adapted to resource-limited healthcare systems.

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Ethical Approval: This study received approval from the Ethics Committee of the School of Public Health, Faculty of Medicine, University of Kinshasa (approval letter No. ESP/CE/12B/2024 dated February 2, 2024).

Conflicts of Interest: None declared.

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