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Circulating Levels of Calprotectin for Prediction of Disease Severity in Hospitalized COVID-19 Patients

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Background

The role of clinical laboratories in COVID-19 pandemic includes staging, prognostication and therapeutic monitoring of patients infected by SARS-CoV-2. Early identification of patients with a higher risk for severity remains crucial to define an optimal strategy for their management.

Severe cases of COVID-19 are characterized by a cytokine storm that mediates widespread inflammation and multi-organ damage, major cause of disease severity in infected patients. Elevated blood levels of some biomarkers have been identified as outcome-related predictors, including inflammatory markers as C-reactive protein (CRP), ferritin and D-dimer. However, the potential role of other emergent inflammatory biomarkers, such as calprotectin, is less known.

During the inflammatory response, neutrophils and monocytes quickly arrive to the site of inflammation. The heterodimeric protein S100A8/A9, named as calprotectin, is an alarmin mainly derived by both cell types which play a critical role in inflammatory response. In this study, we examined the value of serum calprotectin for prediction of in-hospital mortality and need of mechanical ventilation (MV) in hospitalized COVID-19 patients.

Methods

Study design and population: prospective observational study including hospitalized patients with SARS-CoV-2 infection, confirmed either by a positive result of RT-PCR testing of a nasopharyngeal swab specimen or by positive result of serological testing and a clinically compatible presentation.

Blood collection and laboratory tests: on admission to ED, blood samples were drawn for D-dimer, CRP, ferritin and calprotectin levels measurement.

Serum calprotectin levels were measured by a particle enhanced turbidimetric immunoassay (PETIA) (Gentian AS, Norway) on a Cobas c 501 instrument (Roche Diagnostics, Mannheim, Germany), according to manufacturers´ recommendations. For the other biomarkers the following methodologies and analyzers were used: CRP: turbidimetry; Cobas c analyzer; ferritin: turbidimetry; Cobas c analyzer; D-dimer: immunoturbidimetry (DD HS 500 Hemosil), ACL TOP Werfen

Outcomes: need for mechanical ventilation and in-hospital mortality.

Statistical analysis: The discrimination ability for those biomarkers that showed a significant difference between groups, defined according to the endpoints, was evaluated by Receiver Operating Characteristic (ROC) curve analysis (Hanley&Mc Neil method). We used a binary non-adjusted logistic regression model for the prediction of outcomes entering each biomarker dichotomized according to the optimal threshold maximizing the Youden index. The p-values < 0.05 were considered statistically significant. Software package SPSS version 20 (SPSS Inc., Chicago, USA) was used for statistical analyses.

Results

From March 14th to April 12th, 66 consecutive patients were admitted to our hospital with confirmed SARS-CoV-2 infection.

In our cohort, the mortality rate was 12.1% (8/66) and 9 (13.3%) patients required mechanical ventilation. Table 1 shows the differences in demographics and comorbidities between survivors and non-survivors.

For in-hospital mortality, calprotectin showed a good discrimination capacity (Figure 1), as assessed by the analysis of the AUC of ROC curve for in-hospital mortality, similar to both d -dimer and CRP. For calprotectin, optimal cutoff to predict in-hospital mortality was 3.9 mg/L and unadjusted Odd Ratio for this outcome was 13.30 (1.53–116); p = 0.004.

For mechanical ventilation, significant differences were detected for CRP, ferritin and calprotectin, but not for D-dimer (Table 2). Calprotectin, CRP and ferritin showed a significant accuracy for this outcome, with ROC AUC above 0,7 (Figure 2). For calprotectin, optimal cutoff to predict need for mechanical ventilation was 2.3 mg/L and unadjusted Odd Ratio for this outcome was 1.257 (1.082-1.460); p = 0.022. No patient with a serum calprotectin ≤ 2.3 mg/L required mechanical ventilation.

Table 1. Characteristics of COVID-19 patients on admission

	Total population n=66	Survivors n= 58 (87.9%)	Non-survivors n= 8 (12.1%)	p
Age, years [Mean (SD)]	61 (16)	60 (16)	74 (9)	0.013
Age ≥ 70 years	23 (34.8)	17 (29.3)	6 (75)	0.011
Gender, male [n (%)]	43 (65.2)	35 (57.7%)	8 (67.7%)	0.027
Comorbidities				
Hypertension [n (%)]	31 (47.0)	23 (39.7)	8 (100)	0.001
Diabetes mellitus [n (%)]	18 (27.3)	13 (22.4)	5 (62.5)	0.017
Non-asthma respiratory disease [n (%)]	5 (7.6)	4 (6.9)	1 (12.5)	0,574
Cardiovacular disease [n (%)]	15 (22.7)	10 (17.2)	5 (62.5)	0.004
Chronic kidney disease [n (%)]	8 (12.1)	1 (1.7)	7 (100)	<0.001
Immunosupression [n (%)]	6 (9.1)	6 (10.3)	0 (0)	0.340
Laboratory findings on admission				
CRP (mg/dL) [Median (IQR)]	6.9 (3.6-11.8)	6.0 (2.8-10.8)	19.3 (10.4-30.5)	0.008
Ferritin (ng/mL) [Median (IQR)]	382 (254-1256)	360 (223-1256)	769 (501-1301)	0.080
D dimer (ng/mL FEU) [Median (IQR)]	609 (454-935)	570 (404-848)	3465 (995-4432)	0.001
Calprotectin (mg/L) [Median (IQR)]	3.4 (1.9-5.0)	3.1 (1.9-4.4)	7.1 (4.5-10.3)	0.005

Table 2. Laboratory findings according to need for mechanical ventilation

	Non-mechanical ventilation n= 57 (86.7%)	Mechanical ventilation n= 9 (13.3%)	p
Laboratory findings on admission			
CRP (mg/dL) [Median (IQR)]	6.0 (2.8-10.9)	10.1 (7.5-29.7)	0.048
Ferritin (ng/mL) [Median (IQR)]	362 (223-872)	1201 (643-1526)	0.036
D dimer (ng/mL FEU) [Median (IQR)]	600 (457-897)	630 (404-1044)	0.695
Calprotectin (mg/L) [Median (IQR)]	3.2 (1.8-4.8)	5.0 mg/L (3.6-8.4)	0.032

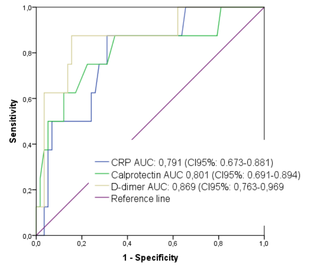

Figure 1. ROC AUC for in-hospital mortality

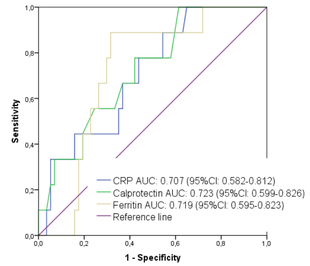

Figure 2. ROC AUC for mechanical ventilation

Limitations

This study has some limitations, namely the small sample size. Hence, we did not perform multivariable analysis, due to the small number of included patients and outcomes. However, the aim was not to generate a predictive model, but rather to explore the potential role of this novel biomarker.

Conclusion

In our study, only CRP and calprotectin showed a significant ability to predict both outcomes. Our findings suggest that calprotectin might have a potential role as an early marker for risk stratification of COVID-19 patients. As one of the earliest biomarkers for neutrophil activation, calprotectin is of special interest for early identification of patients at the risk for development of severe events and mortality. Further investigations are required to confirm our preliminary findings.