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Routine laboratory tests for risk stratification of COVID-19 patients discharged from the Emergency Department

Biomarcadores clásicos para la estratificación del riesgo de pacientes con COVID-19 dados de alta desde el Servicio de Urgencias

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ABSTRACT

Objetive: to evaluate the value of canonical biomarkers for prognosis of COVID-19 patients discharged from Emergency Department (ED) to home for ambulatory management.

Methods: single-center study. Primary outcome was the return hospital admission.

Results: population study included 145 patients. 19 (13.1 %) patients re-visited ED requiring admission to hospital. LDH was the biomarker with the highest discriminatory ability for outcome. The hospitalization was associated with elevated LDH activity and creatinine levels and decreased sodium levels.

Conclusion: canonical biomarkers as LDH might have a role for prognosis in seemingly stable COVID-19 patients.

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RESUMEN

Objetivo: evaluar la utilidad de biomarcadores clásicos para el pronóstico de pacientes con COVID-19 dados de alta desde el Servicio de Urgencias (SU) para manejo ambulatorio.

Métodos: estudio unicéntrico. La revisita a urgencias con ingreso hospitalario fue definida como el evento principal.

Resultados: la población de estudio incluyó 145 pacientes, de los que 19 (13,1 %) regresaron al SU y requirieron ingreso hospitalario. La LDH fue el biomarcador con mayor capacidad discriminatoria. La hospitalización estuvo asociada con el incremento de LDH y creatinina y descenso de sodio.

Conclusión: biomarcadores como la LDH pueden tener utilidad para el pronóstico de pacientes con COVID-19 aparentemente estables.

INTRODUCTION

The role of clinical laboratories in COVID-19 pandemic includes staging, prognostication and therapeutic monitoring. Hence, numerous laboratory tests have been identified as outcome-related predictors in hospitalized patients (1), but their usefulness for a a safe discharge of seemingly stable COVID-19 patients admitted to an Emergency Department (ED) has been scarcely studied.

Because in the current context of high transmissibility, less severity and high rate of vaccinated individuals, to identify which patients can be safely discharged to home for self-isolation is a challenge for ED physicians (2), we evaluated the role of canonical biomarkers for short-term (14 days) risk stratification of COVID-19 patients discharged from ED.

MATERIALS AND METHODS

Study design and patients

This was a single-center prospective observational study recruiting symptomatic and laboratory-confirmed adult COVID-19 patients admitted to the ED of our hospital from November 29 2021 to January 13 2022 and discharged to home for ambulatory care. Exclusion criteria were: 1) patients with criteria for hospital admission, but requiring self-discharge from the ED; 2) pregnant women, and 3) follow-up not feasible or lack of social support for ambulatory care. The criteria for ED discharge were the presence of stability hemodynamic and the absence of respiratory insufficiency, defined as respiratory rate ≤ 24 breaths per minute and oxygen saturation ≥ 94 %.

The study was approved by the local Ethics Committee (E.O.2020-38 LAB2-COVID19) and performed under a waiver of informed consent, because samples were not collected for research purpose (3), and in accordance with the Declaration of Helsinki.

The primary outcome was the return hospital admission, defined as an unscheduled return ED visit for COVID-19-related symptoms requiring hospitalization within 14 days from discharge.

Variables to collect

For eligible patients, health records underwent individual chart review by a ED physician to extract the following data, selected from literature (4-12): demographics, previous comorbidities, laboratory tests on admission to ED, vaccination status and outcome data.

Laboratory assays

Samples were analysed for sodium and potassium ions, by indirect potenciometry on Cobas ISE analyzer (Roche Diagnostics, Switzerland); creatinine, by a colorimetric assay (Jaffe reaction); C-reactive protein (CRP), by an immunoturbidimetric assay; lactate dehydrogenase (LDH), by an ultraviolet assay (lactate to pyruvate, traceable to IFCC method) and alanine aminotransferase (ALT), by a method according to IFCC without pyridoxal phosphate activation, on Cobas c702 (Roche Diagnostics, Switzerland) platform; procalcitonin by a chemiluminiscent enzyme immunoassay on G600II analyzer (Fujirebio Diagnostics Inc. Japan); D-dimer, by immunoturbidimetry on ACL-TOP Family (Instrumentation Laboratory, US) analyzers; and cell blood count by flow cytometry on Sysmex XN (Sysmex, Japan) analyzers (13).

Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov or Shapiro-Wilk tests, as appropriate. Data were described as numbers and percentages for categorical variables and as medians (interquartile ranges [IQR]) or mean (standard deviation [SD]) for continuous data. Comparisons between groups were performed with chi-square or Fisher tests

for categorical data and Mann-Whitney U or t-Student tests for continuous data, as appropriate. Areas under the receiver operating characteristic (ROC) curve (AUC) were calculated as a measure of the discriminatory ability for the outcome and optimal cut-offs were defined as the value maximizing the Youden index. We also investigated the association of biomarkers with the endpoint reporting odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

Statistical analysis was performed using SPSS vs. 22 (SPSS Inc) and MedCalc 15.0 (MedCalc Software). Statistical significance was set at 5 %.

RESULTS

During the enrolment period, 160 COVID-19 patients were recruited. Finally, before exclusion criteria were applied, the study population included 145 COVID-19 patients discharged from the ED for ambulatory follow-up. Revisits to the ED within 14 days occurred for 41/145 (28.3 %) of patients and returns resulting in hospitalization within 14 days occurred in 19/145 (13.1%) of patients. A summary of the results is provided in table I.

Focusing on laboratory findings, creatinine, procalcitonin, CRP, ALT, LDH, were significantly higher and, in contrast, sodium significantly lower, in patients revisiting the ED and requiring admission to hospital (Table I). We also investigated which baseline factors were associated with our primary endpoint by means of discrimination and association. For discrimination, LDH was the biomarker with the highest ROC AUC, greater than 0.8 (Table II) (Fig. 1). Optimal cutoffs are listed in table III (LDH: 237 U/L, creatinine: 76.91 mmol/L , procalcitonin: 0.06 mg/L, ALT: 21 U/L and CRP: 14.8 mg/L) achieving all of them a high negative predictive value, greater than 95%, to rule-out the outcome. Finally, only LDH, creatinine and sodium were associated in univariate analysis with the primary outcome (Table II).

Of note, those patients revisiting the ED but not requiring admission to hospital (n = 22) showed lower levels than the selected cutoffs for LDH, creatinine, CRP, procalcitonin and ALT.

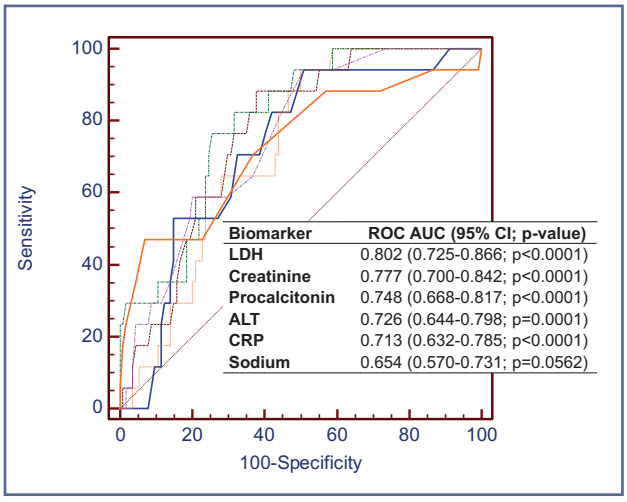

Figure 1 – *ROC curves of biomarkers for outcome.*

Table I.
Baseline characteristics in overall population and in groups according to return hospital admission

	All patients n = 145	Non-return hospital admission n = 126 (86.9 %)	Return hospital admission n = 19 (13.1 %)	*p*
Age (years), mean (DE)	51.3 (16.8)	50.9 (17.4)	54 (11.6)	0.449
Sex, male (n [%])	75 (51.7)	60 (47.6)	15 (78.9)	*0.011*
Vaccination stage, vaccinated (n [%]) Vaccinated Non-vaccinated	 92 (63.4) 53 (36.6)	 87 (69.0) 39 (31.0)	 5 (26.3) 14 (73.7)	*< 0.001*
Time from symptom onset (days), median (IQR)	4 (2-7)	3 (1-7)	5 (4-7)	*0.028*
Time from discharge to ED revisit (days), median (IQR)	3 (2-5)	-	-	-
Comorbidities, n (%)				
Hypertension	45 (31.0)	37 (29.4)	9 (42.1)	0.263
Diabetes *mellitus*	20 (13.8)	17 (13.5)	3 (15.8)	0.728

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Table I (cont.)
Baseline characteristics in overall population and in groups according to return hospital admission

	All patients n = 145	Non-return hospital admission n = 126 (86.9 %)	Return hospital admission n = 19 (13.1 %)	*p*
Rheumatologic diseases	9 (6.2)	9 (7.1)	0	0.272
COPD or other chronic respiratory diseases	17 (11.7)	16 (12.7)	1 (5.3)	0.310
Cardiovascular disease	15 (10.3)	12 (9.5)	3 (15.8)	0.310
Chronic kidney disease	9 (6.2)	6 (4.8)	3 (15.8)	0.096
Active cancer	5 (3.4)	3 (2.4)	2 (10.5)	0.128
Immunosupression	9 (6.2)	6 (4.8)	3 (15.8)	0.096
Laboratory findings				
Creatinine (mmol/L)	74.3 (58.4-92.8)	71.6 (57.5-85.8)	97.2 (84.0-106.1)	*<0.001*
Sodium (mmol/L)	139 (137-141)	139 (138-141)	138 (134-139)	*0.030*
Potassium (mmol/L), n = 139	4.2 (3.9-4.5)	4.2 (3.9-4.5)	4.3 (4.1-4.5)	0.495
ALT (U/L), n=140	22 (15-34)	21 (15-31)	41 (25-47)	*0.003*
LDH (U/L), n=136	211 (169-263)	206 (166-243)	264 (246-387)	*<0.001*
CRP (mg/L)	17.3 (6.1-45.3)	15.1 (5.4-33.2)	38.4 (18.2-58.0)	*0.003*
Procalcitonin (mg/L), n = 142	0.06 (0.04-0.11)	0.06 (0.03-0.10)	0.12 (0.07-0.15)	*0.001*
WBC count (*10^9/L)	6.27 (4.75-8.09)	6.23 (4.72-8.30)	6.51 (5.70-7.81)	0.688
Neutrophil count (*10^9/L)	4.19 (2.83-5.49)	3.95 (2.67-5.49)	4.47 (3.77-5.61)	0.302
Lymphocyte count (*10^9/L)	1.33 (0.98-1.82)	1.38 (1.01-1.87)	1.16 (0.98-1.31)	0.110
NLR	3.1 (2.1-4.9)	2.9 (2.0-4.8)	4.02 (3.1-5.2)	0.058
Platelet count (*10^9/L)	205 (170-252)	209 (170-255)	179 (169-200)	0.097
D-dimer (ng/mL FEU), n = 139	457 (272-713)	469 (271-749)	440 (319-655)	0.979

ED: Emergency Department; IQR: Interquartile range; DE: deviation standard; COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; LOS: length of stay (days); LDH: lactate dehydrogenase; ALT: alanine aminotransferase; CRP: C-reactive protein; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio.

Table II.
Analysis of discriminatory ability and association of biomarkers with the primary endpoint

Biomarker	ROC AUC (95 CI %; *p*)	Univariate OR (95 % CI; *p*)
LDH	0.802 (0.725-0.866; *p < 0.0001*)	1.015 (1.007-1.022; *p < 0.001*)
Creatinine	0.777 (0.700-0.842; *p < 0.0001*)	4.963 (1.382-17.820; *p = 0.014*)
Procalcitonin	0.748 (0.668-0.817; *p < 0.0001*)	1.149 (0.359-1.149; *p* = 0.815)
ALT	0.726 (0.644-0.798; *p = 0.0001*)	1.011 (0.994-1.029; *p* = 0.220)
CRP	0.713 (0.632-0.785; *p < 0.0001*)	1.120 (0.988-1.270; *p* = 0.077)
Sodium	0.654 (0.570-0.731; *p* = 0.0562)	0.801 (0.677-0.948; *p = 0.010*)

Only biomarkers with a significant difference between groups were included in the analysis. ROC: receiver operating characteristics; AUC: area under the curve; CI: confidence interval; OR: odd ratio; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; CRP: C-reactive protein.

Table III.
Accuracy of biomarkers for predicting return hospital admission

Biomarker	Cutoff*	Sensitivity (95 CI %)	Specificity (95 CI %)	Positive predictive value (95 CI %)	Negative predictive value (95 CI %)
LDH	237 U/L	82.4 (56.6-96.2)	69.8 (60.7-77.8)	28.0 (16.2-42.5)	96.5 (90.1-99.3)
Creatinine	76.91 mmol/L	89.5 (66.9-98.7)	59.5 (50.4-68.2)	25.0 (15.3-37.0)	97.4 (90.9-99.7)
Procalcitonin	0.06 mg/L	94.4 (72.7-99.9)	50.0 (40.9-59.1)	21.5 (13.0-32.3)	98.4 (91.4-100)
ALT	21 U/L	94.1 (71.3-99.9)	48.8 (39.7-58.0)	20.3 (12.0-30.8)	98.4 (91.2-100)
CRP	14.8 mg/L	94.7 (74.0-99.9)	49.2 (40.2-58.3)	22.0 (13.6-32.5)	98.4 (91.4-100)

*Optimal cut-off according to Index Youden. CI: confidence interval; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; CRP: C-reactive protein.

DISCUSSION

Similar to other infectious diseases, an early diagnosis and assessment of severity is therefore key in order to initiate triaging and appropriate therapeutic strategies in patients infected by SARS-CoV-2. Hence, trying to identify those that could be safely discharged from ED for ambulatory care would avoid the admission of patients with uncomplicated infections who are at no further risk of disease progression that subsequently leads to extra clinical workload and financial burden. The use of laboratory tests for assessing disease severity may therefore be of great clinical interest in order to facilitate improved triaging and earlier therapeutic decisions.

Recent studies have reported the association between the need for hospitalization among COVID-19 patients initially discharged from ED for ambulatory care and differents factors, including time from onset of symptoms, demographics such as age ≤ 48 years, symptoms such as fever and comorbidities such as COPD, hypertension, cognitive impairment, diabetes *mellitus,* coronary artery disease and chronic kidney disease (6,7,11,12). Although some studies have reported the value of emerging biomarkers, such as soluble urokinase plasminogen activator receptor (suPAR) and mid-regional pro-adrenomedullin (MR-proADM), for a safe discharge of COVID-19 patients in an ED (9,14), the role of canonical biomarkers usually available in STAT laboratories is less known. Hernández-Biete *et al.* identified a lymphocyte count < 1.0 *10^9 as predictor for hospitalization afterwards (4). In a similar study, admission was associated with elevated LDH and creatin-kinase levels and lymphopenia (12). Moreno-Pérez *et al.* (15) have also reported significant higher CRP, procalcitonin, LDH, and potassium levels and lower lymphocyte count in mild COVID-19 patients initially discharged from ED and admitted to hospital later. In Menditto *et al.* study, patients requiring a return hospital admission had higher procalcitonin and D-dimer levels and neutrophilia was a major predictor of return hospital admission (7). Our results confirm the potential role of some canonical biomarkers for predicting revisit to the ED and hospital admission. Inflammatory biomarkers such as LDH achieved a high discriminatory ability for the outcome, with ROC AUC above 0.8.

This study has some limitations. First, the sample size was small and a previous estimation was not calculated, limiting the fastness of our findings. Second, due to preanalytical interferences for measurement of some biomarkers, such as hemolysis for potassium, ALT, LDH or D-dimer, not all evaluated laboratory parameters were available for all patients, resulting in some missing data. Also, only association for biomarkers and outcome was studied and we did not perform multivariable analysis due to the small sample size and number of outcomes. However, the main purpose was not to derive a multivariable prediction model, including demographics, comorbidities and other variables, but rather to identify potential easily available biomarkers for risk-stratification of COVID-19 patients discharged from ED. Hence, we strongly encourage such an effort performing multicenter surveys, which would be much more generalizable.

In conclusion, in apparently stable COVID-19 patients discharged from ED, canonical blood biomarkers such as LDH might be used as support tools to help clinicians. Further investigations are needed in order to develop risk stratification tools including these biomarkers and other variables, which help physicians to choose the better disposition for patients with COVID-19 in the ED.

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