

A simple tool to help ruling-out Covid-19 in the emergency department: derivation and validation of the LDH-CRP-Lymphocyte (LCL) score

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Abstract

After the outbreak of the Covid-19 pandemic, cases of SARS-CoV-2 infections may gradually decrease in the next months. Given the reduced prevalence of the disease, Emergency Departments (ED) are starting to receive more and more non-Covid19 patients. Thus, a way to quickly discriminate ED patients with potential Covid-19 infection from non-Covid19 patients is needed in order to keep potentially contagious patients isolated while awaiting second-level testing. In this paper, we present the derivation and validation of a simple, practical, and cheap score that could be helpful to rule out Covid-19 among ED patients with suspicious symptoms (fever and/or dyspnoea). The LCL score was derived from a cohort of 335 patients coming to the ED of our hospital from March 16th to April 1st, 2020. It was then retrospectively validated in a similar cohort of 173 patients admitted to our ED during April. The score is based on blood values of lactate dehydrogenase, C-reactive protein, and lymphocyte count. The LCL score performed well both in the derivation and in the validation cohort, with an AUC respectively of 0.81 (95% CI: 0.77 – 0.86) and of 0.71 (95% CI: 0.63 – 0.78), given the difference in Covid-19 prevalence between the two cohorts (57% vs 41% respectively). An LCL score equal to 0 had a negative predictive value of 0.92 in the derivation cohort and of 0.81 in the validation cohort, with a negative likelihood ratio respectively of 0.08 and 0.36 for Covid-19 exclusion. This score could, therefore, constitute a useful tool to help physicians manage patients in the ED.

Introduction

Since the outbreak of the Covid-19 pandemic, Emergency Departments (ED) had to redefine their working routine and the management of patients with symptoms suggestive for Covid-19 (e.g. dyspnoea and fever). The *Santa Croce e Carle* Teaching Hospital in Cuneo is a hub hospital for a population of more than 580,000 inhabitants. Since the first cases of SARS-CoV-2 infection recorded in our area on March 8th, 2020, a *dirty* red area has been set up in our ED where patients with symptoms suggestive for Covid-19 have been examined. Thanks to restrictive lockdown measures, as weeks passed, we have observed a drop in the diagnosis of new Covid-19 cases. However, we shortly expect a period in which there will not only be *clean* and *dirty* patients but a group of *grey* patients with suspicious symptoms: in these cases, our goal will be to exclude the presence of SARS-CoV-2 infection in a fast and safe way.

This paper describes the derivation and validation of a simple, practical score based on a few blood tests values capable of discriminating patients with probable Covid-19 among the ones with suggestive symptoms. This score aims to identify patients in need of testing for SARS-CoV-2 infection and patients who should remain isolated and considered potentially at-risk until further investigation.

Material and Methods

We retrospectively analysed the diagnostic performance of different blood tests in predicting the presence of SARS-CoV-2 infection in a cohort of consecutive patients admitted to the ED with symptoms suggestive for Covid-19 (presence of at least one among fever and dyspnoea) from March 16th to April 1st 2020 (derivation cohort). Blood sample and nasopharyngeal swab were taken at the time of admission to the ED. Real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) analysis was considered the gold-standard method for the diagnosis.

Based on this first cohort, we created a score that we retrospectively validated in a second similar cohort of consecutive patients admitted to the ED with symptoms suggestive for Covid-19 during April (validation cohort). Variables included in the score were chosen among ED-available blood test that significantly differed between Covid-19 and non-Covid-19 patients. The score thresholds were identified through the analysis of the Receiver Operating Characteristic (ROC) curves. A logistic regression model confirmed that the variables included in the score were independently associated with swab result. Continuous variables are expressed as median and interquartile range and compared with the Mann-Whitney U-test. The diagnostic performance of the parameters was evaluated in terms of sensitivity, specificity, negative predictive value, positive predictive value, positive likelihood ratio and neg-

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ative likelihood ratio. The local ethics committee approved the study (ID: MED.URG10). The statistical analysis was performed with the *R* software.

Results

From March 16th to April 1st, 2020, 335 consecutive patients presented to the ED with symptoms suggestive for Covid-19 (median age 69 years, IQR 56 – 81, male/female ratio 1.2). Among them, 189 (57%) had a positive nasopharyngeal swab. Of the 146 (43%) non-Covid patients, 57 (39%) were discharged from ED, and the most frequent discharge diagnoses were upper respiratory tract infection (39%), fever (17%), diarrhoea (10%). The 89 (61%) non-Covid patients admitted to a ward had sepsis (27%), heart failure (19%), non-Covid pneumonia (15%), chronic obstructive pulmonary disease exacerbation (7%) and acute coronary syndrome (2%). In-hospital mortality rate among Covid-19 and non-Covid-19 patients was very similar (11,6% and 10,9% respectively). No patient with negative swab tested positive on a second test. Variables included in the score showed significant differences between Covid-19 and non-Covid-19 patients (Table 1). C-

Reactive Protein (CRP), Lactate Dehydrogenase (LDH) and lymphocyte count showed an Area Under the Curve (AUC) of 0.70 (95% CI: 0.65 – 0.76), 0.77 (95% CI: 0.71 – 0.82) and 0.67 (95% CI: 0.61 – 0.73) respectively (Figure 1). These parameters (1 point assigned for each) were thus included in the LCL score (LDH, CRP, Lymphocyte), with threshold values of >268 U/l for LDH, >21.78 mg/dl for CRP and <1600 cells/ μ l for lymphocyte count (threshold values were chosen by analysing the AUCs). The AUC of the score was 0.81 (95% CI: 0.77 – 0.86), (Figure 2). In a logistic regression model, the variables of the score were independent predictors of the swab result (Table 2). The presence of every score variable (LCL score = 3) showed a sensitivity of 0.63 and a specificity of 0.88. The positive predictive value was 0.86, the negative predictive value was 0.66, the positive likelihood ratio was 5.23, and the negative likelihood ratio was 0.42. An LCL score = 0 (*i.e.* absence of all variables) showed a negative predictive value of 0.92, and a negative likelihood ratio of 0.08.

The validation cohort consisted of 173 patients admitted to the ED during April and was similar to the derivation cohort, showing no significant differences in demographic characteristics (median age 72 years old, IQR 54-85, male/female ratio 1.1). 41% of patients had positive nasopharyngeal swab for SARS-CoV-2. In this cohort, the AUC of the score was 0.71 (95% CI: 0.63 – 0.78).

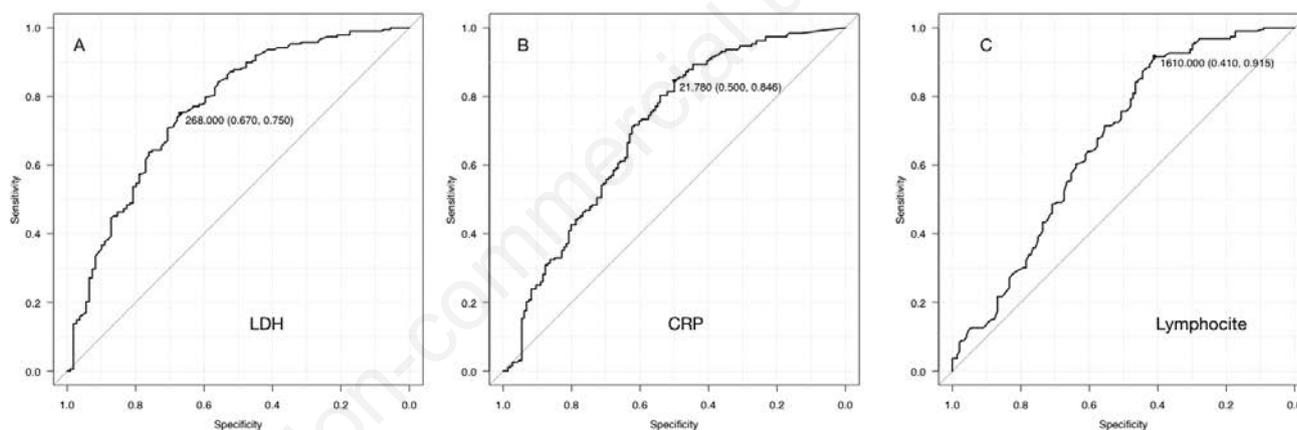


Figure 1. Receiver Operating Characteristic (ROC) curves of lactate dehydrogenase (LDH), C-reactive protein (CRP) and lymphocyte count.

Table 1. LCL score variables differences between Covid and non-Covid patients. Data were showed as median [range].

	All patients (n= 335)	Non-Covid patients(n=146)	Covid patients(n=189)	p value
Lymphocyte count (cells/ μ l)	940 [600; 1420]	1215 [772; 1795]	890 [570; 1260]	<0.00001
LDH (U/l)	302 [240; 392]	229 [201; 285]	322 [265; 430]	<0.00001
CRP (mg/dl)	62.12 [21.32; 144.8]	27.2 [5.31; 84.8]	78.55 [33.54; 152.21]	0.00008

Table 2. Logistic regression model (McFadden $R^2 = 0.266$) of the variables included in LCL score.

	Odds ratio	95% Confidence interval	P value
Lymphocyte count < 1610 cells/ μ l	4.46	2.25-8.83	< 0.001
LDH > 268 U/l	6.6	3.84-11-31	< 0.001
CRP > 21.78 mg/dl	2.27	1.24-4.11	0.007

The LCL score was 3 in 43% of the patients, with a specificity of 0.92 and a positive likelihood ratio of 5.46. The positive predictive value was 0.78; the negative predictive value was 0.70. An LCL score equal to 0 showed a negative predictive value of 0.81, and a negative likelihood ratio of 0.36.

Discussion

To date, some efforts were made in order to create prognostic models in Covid-19 patients.^{1,2} However, there is no consensus on which tools to use to rule-in and rule-out Covid-19. Kurstjens *et al.* recently developed a model called corona-score to evaluate SARS-CoV-2 infection status of patients presenting at the ED with respiratory symptoms; it includes the same variables of the LCL score and adds some laboratory, demographic and imaging data. High LDH and CRP and low lymphocyte count confirmed to be associated with a higher probability of SARS-CoV-2 infection. In the corona-score, ferritin is included: unfortunately, ferritin dosage is not available in all EDs. Authors state that a score-based approach could reduce RT-PCR testing; we think, indeed, that a score could reduce the practice of *re*-testing, reserving a second swab only to high-risk patients as identified by the model.³ Also, Santotoribio and co-workers identified LDH and CRP as predictors of SARS-CoV-2 infection in patients referring to ED with clinical suspicion of Covid-19.⁴

The LCL score could have several advantages not only in clinical management but also in ED organisation and the decision-making process, allowing to dedicate the *dirty* areas only to patients in which Covid-19 cannot be excluded at an early stage. The strengths of the LCL score are the high negative predictive value and the low negative likelihood ratio that could help exclude the presence of SARS-CoV-2 infection among ED patients with suggestive symptoms. This could be particularly important in the

upcoming months when the prevalence of the disease is likely to decrease and when the EDs will be full of non-Covid-19 patients. For example, among patients with dyspnoea, it will be necessary to rapidly understand which of them could have Covid-19 and which instead need other explanation for their symptomatology. Alterations in the components of the LCL score are common to many serious presentations at the ED, but the presence of all the three items could characterize Covid-19 patients, and most of all their absence (*i.e.* LCL score = 0) could rule-out SARS-CoV-2 infection in the presence of a previous negative swab.

In fact, the context in which LCL may be helpful could be deciding if a second RT-PCR test is needed when the first test has resulted negative. We suggest the primary use of LCL score to determine after the initial swab has resulted negative if the patient needs additional testing or has a low-enough post-test probability that precautions can be removed. So far, in daily experience, a second swab is often obtained in negative patients in which Covid-19 suspicion remains elevated. In this regard, we think that using a score could standardize this process, indicating when non-to perform an unnecessary second swab (*e.g.* in patients with LCL = 0) and when re-testing is appropriate (*e.g.* in patients with LCL \geq 1).

Besides, a score-based approach may be congenial to emergency physicians who are used to such a tool for other diseases (*e.g.* pulmonary embolism, aortic dissection, *etc.*).^{5,6} The LCL score is based on laboratory parameters that are simple, cheap, and quick to obtain. In addition, assigning one point to each component of the score is the most pragmatic and immediate way to use it. These characteristics suit well the context of the ED.

Our score has some limitations. We didn't consider radiological findings to be insert in the score: in fact, in our cohorts, especially lung ultrasound and chest computed tomography were not available for all patients. In addition, RT-PCR itself (the gold-standard test we assumed in this study) has a 70% sensitivity.⁷ Moreover, the score was derived from a single-centre study with a relatively low number of patients and prospective validation should be performed.

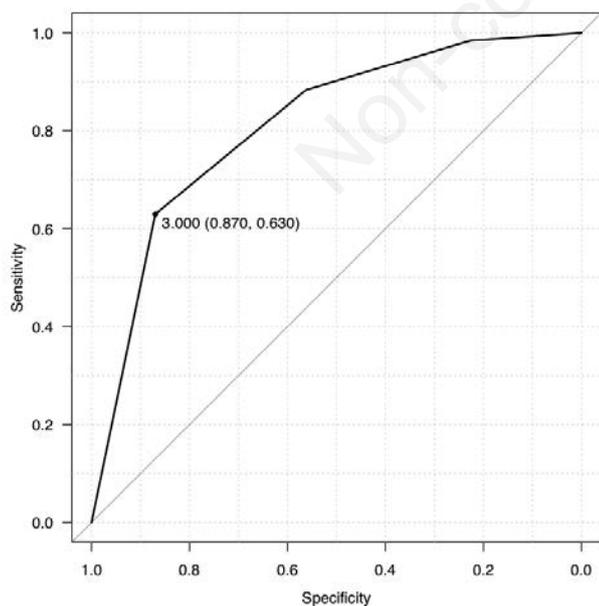


Figure 2. Receiver Operating Characteristic (ROC) curve of LCL score.

Conclusions

The LCL score, including low-cost and straightforward laboratory parameters, showed a good quality performance in helping ED decision-making about patients with suspected Covid-19 infection.

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