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Predictive factors of poor outcomes in the COVID-19 epidemic: Consider the inflammatory response

Dear editor,

We read with interest the article by Wang et al., who assessed the usefulness of CRP levels in the early stage of COVID-19 to correlate with disease severity [1]. They showed that CRP levels were positively correlated with lung lesions and could reflect disease severity.

These findings concurred with our prospective study.

In December 2019, a new coronavirus emerged in Wuhan and rapidly spread through China and all over the world [2]. The pandemic of coronavirus disease 19 (COVID-19) is now responsible for more than 110,000 deaths in 178 countries (as of April 14, 2020), carrying a mortality rate from 3% to 7%.

Clinical presentation is heterogenous from benign presentations to acute respiratory distress syndrome (ARDS) leading to intensive care unit (ICU) hospitalization or death [3,4].

As a small proportion of patients suffer from severe conditions, there is an urgent need for early recognition of factors associated with poor outcome.

The first patient of Besançon University Hospital was identified on March 5, 2020 and from then on, the number of cases has rapidly increased.

We aimed to identify risks factors for poor outcome of COVID-19 infection in hospitalized patients during the first month of the pandemic in Besançon University Hospital.

We retrieved records of patients hospitalized during the first month of the pandemic. Patients were hospitalized if they suffered from non-tolerable high-grade fever, shortness of breath or chest pain. Each COVID-19 diagnosis was confirmed using real-time reverse transcriptase polymerase chain reaction on nasopharyngeal samples.

Oxygenation support was introduced for every patient with oxygen saturation (spO_2) below 94%. Every patient received first-line antibiotics for community-acquired pneumonia at admission. At the beginning of the study, no specific drugs were used to treat COVID-19 in our center.

All patients received complete laboratory tests at admission, including acute phase reactants (i.e., C-reactive protein [CRP], procalcitonin [PCT], ferritin, fibrinogen), complete blood count, liver, and kidney function tests.

Poor outcome was defined by transfer to the ICU and/or death.

The study was conducted in accordance with the international review board of the institution.

A total of 52 patients were included with a mean age of 65.3 ± 19.2 years with no difference between the two groups ($P = 0.69$).

The mean duration between symptom onset and hospitalization was approximately 5.18 ± 4.22 days in both groups ($P = 0.51$). A total of 28 patients received oxygenation therapy; all patients without oxygenation support underwent physical examination or imaging demonstrating pneumonia. High levels of CRP, PCT, AST, and LDH were associated with poor outcome (Table 1). However, CRP levels had the best accuracy (area under the curve 0.808) to predict poor outcome (Fig. 1). CRP levels at 31.5 mg/L had sensitivity of 91% and specificity of 43%, whereas CRP levels at 98 mg/L had sensitivity of 67% but specificity of 80%.

Ferritin levels appeared to be more elevated in the poor outcome group but were not significant ($P = 0.11$).

No difference regarding blood counts and kidney/liver function was predictive of admission to the ICU or death (Table 1).

COVID-19 has avidity for the respiratory tract and can induce ARDS in some patients. Our data confirms data from China showing that there is no initial kidney or liver failure [2–4]. The increase in AST levels is probably related to cell lysis and rhabdomyolysis, irrespective of ALT levels.

We identified a group of patients with high inflammatory response associated with poor outcomes. As very low bacterial co-infection is reported in COVID-19, we hypothesized that inflammation was virus-related. CRP levels were the best predictive biological factors associated with poor outcome. Despite no statistical relevance in our study, high ferritin levels have already been described as predictor of acute respiratory distress syndrome [5]. Recent studies found that decreased lymphocyte counts and increased D-dimer concentrations might be an indication of negative prognosis. In addition, several biomarkers such as decreased albumin levels as well as elevated creatine kinase levels and higher LDH levels were associated with poor outcome of COVID-19 [6]. For those patients, the therapeutic approach including antiviral and/or anti-inflammatory treatments (steroids, IL-6 blockers, IL-1 blockers) should be initiated to avoid ARDS [7–9]. Moreover, hemophagocytic lymphohistiocytosis has to be considered in patients with high ferritin levels.

There are some limitations to this study. First of all, it is a retrospective study with data collection based on the information available on the patient's records. Moreover, all patients hospitalized did not have standard complete biology performed at the beginning of the pandemic.

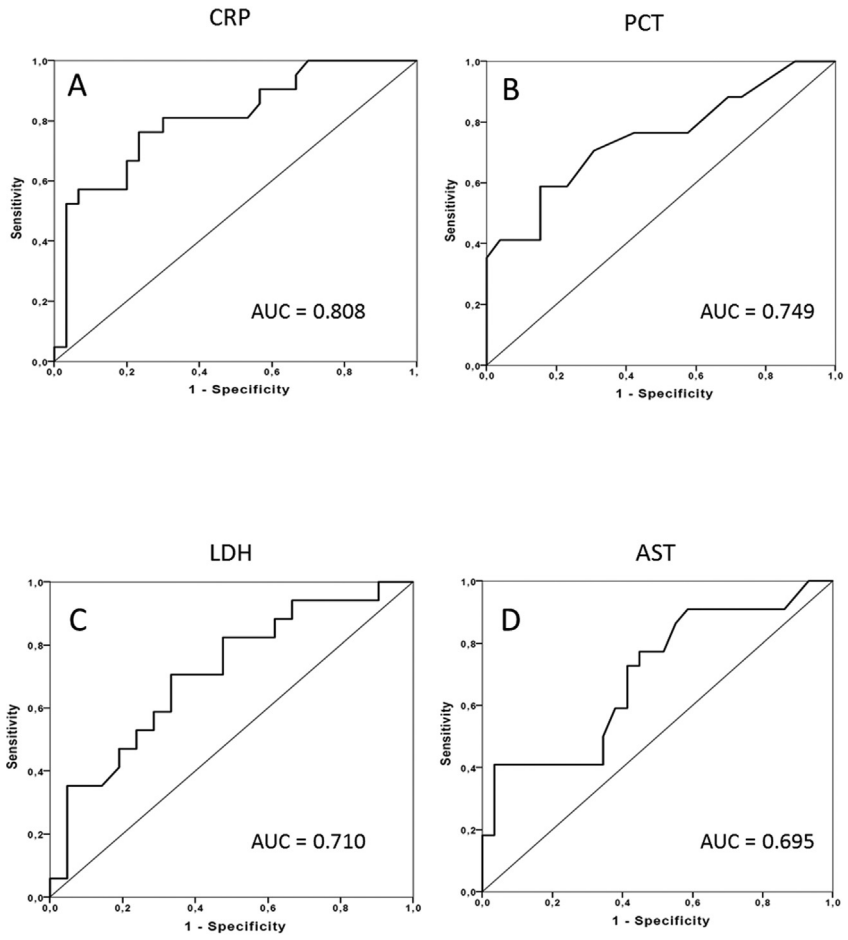
Our major strength is that data was derived from a tertiary care center in Europe with high prevalence of COVID-19 infection.

This data suggests simple laboratory test (CRP) to stratify the risk of poor outcome and guidance to therapeutic approach.

Table 1
Characteristics of patients hospitalized with COVID-19 infection (mean ± SD).

	TOTAL	Favorable outcome ($n = 30$)	Poor outcome ($n = 22$)	P-value
Age	65.3 (±19.2)	63.6 (±22.5)	67.5 (±13.6)	0.69
ALT (IU/L)	39.8 (±34.9)	31.8 (±18.3)	50.8 (±47.7)	0.14
AST (IU/L)	62.7 (±88.3)	42.2 (±16.9)	89.8 (±130)	0.018
Bilirubin (μmol/L)	8.57 (±4.03)	8.12 (±3.23)	9.14 (±4.86)	0.79
Creatinine (μmol/L)	98.8 (±86.7)	84.9 (±34.0)	118 (±126)	0.2
CRP (mg/L)	99.5 (±101)	57.4 (±63.4)	160 (±114)	< 0.001
Ferritin (ng/mL)	1,156 (±1,353)	849 (±701)	1,574 (±1,857)	0.11
Fibrinogen (mg/L)	5.96 (±1.60)	5.90 (±1.79)	6.03 (±1.43)	0.91
Hemoglobin (g/dL)	13.1 (±1.85)	13.2 (±1.90)	12.9 (±1.80)	0.5
Platelets (G/L)	202 (±86.3)	204 (±97.4)	199 (±71.1)	0.88
Leucocyte counts (G/L)	6.13 (±2.42)	5.91 (±2.16)	6.43 (±2.76)	0.74
Lymphocyte counts (G/L)	0.970 (±0.462)	1.03 (±0.435)	0.871 (±0.497)	0.1
PCT (ng/mL)	0.559 (±1.67)	0.151 (±0.759)	1.18 (±2.58)	< 0.01
LDH (IU/L)	407 (±198)	350 (±148)	478 (±231)	0.029

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; PCT: procalcitonin; LDH: lactate dehydrogenase.



CRP value (mg/L)	Sensitivity	1-specificity
0,00	1,00	1,00
2,00	1,00	0,97
3,50	1,00	0,90
5,00	1,00	0,87
8,00	1,00	0,80
10,50	1,00	0,77
11,50	1,00	0,73
13,00	1,00	0,70
15,00	0,95	0,67
18,50	0,91	0,67
24,50	0,91	0,63
29,50	0,91	0,60
31,50	0,91	0,57
36,50	0,86	0,57
41,50	0,81	0,53
44,50	0,81	0,50
47,50	0,81	0,43
49,00	0,81	0,40
52,50	0,81	0,37
56,50	0,81	0,33
63,00	0,81	0,30
69,00	0,76	0,30
73,00	0,76	0,23
85,50	0,71	0,23
96,00	0,67	0,23
98,50	0,67	0,20
102,50	0,62	0,20
107,50	0,57	0,20
115,50	0,57	0,17
123,50	0,57	0,13
130,50	0,57	0,10
137,50	0,57	0,07
147,50	0,52	0,07
158,00	0,52	0,03
166,50	0,43	0,03
179,00	0,38	0,03
187,50	0,33	0,03
198,00	0,29	0,03
232,00	0,24	0,03
261,50	0,19	0,03
278,50	0,14	0,03
293,50	0,10	0,03
297,50	0,05	0,03
389,00	0,05	0,00
480,00	0,00	0,00

Fig. 1. Receiver operating characteristic (ROC) curves for CRP (A), PCT (B), LDH (C), and AST (D) in the prediction of poor outcome. AUC: area under the curve.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Contribution

JR, KB, CC, and SH designed the study. JR, KB, and LM collected the data and wrote the initial draft. KB performed the statistical analysis. All authors contributed to editing the article, and approved the final version of the article.

Disclosure of interest

The authors declare that they have no competing interest.

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COVID reverse transcriptase PCR in private laboratories: From theory to reality

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1. Introduction

In the COVID-19 epidemic context, because of the shortage of diagnostic RT-PCR tests (reverse transcription-polymerase chain reaction), the French public health strategy as of April 7, 2020 is to obtain as many positive tests as possible to be able to follow the epidemic evolution. Thus, the use of tests has been restricted. They are performed with nasopharyngeal samples, which sensitivity is moderate (70%) [1]. In real conditions though, can the prescription relevance and the sampling quality influence these results?

2. Methodology

This cross-sectional study was based on COVID-19 RT-PCR tests performed at the Dynabio laboratory, a group of five laboratories in Rillieux-la-Pape, Lyon and Meyzieu (Rhône), France. They were carried out in a polyclinic, a medicalized nursing home, and in outpatient settings. Samples were analyzed by EUROFINS CBM69 Médipole laboratory.

Sampling was performed by the biologist within the laboratory, by previously trained nurses within the polyclinic, and by a member of the health care team within the medicalized nursing home.

As per recommendations, tests were reserved to patients with COVID-19 evocative symptoms such as respiratory or general symptoms (fever, asthenia, stiffness), and with one of the following criteria [2]: severe symptoms (hospitalization), severe risk factors, health care workers, pregnancy, exploration of an infection source in a community setting.

For outpatients, prescribers had to fill in a medical questionnaire to document these indications. Given the difficulty to perform this on the Lafayette site (Lyon), biologists had to collect samples exclusively at home and thus had to strictly control the prescription relevance. They prioritize situations for which a positive test would induce a change in the patient care, relying on the presence of fever and respiratory disorders, contact with a confirmed COVID-19 case, and health care workers.

Tests performed between March 12 and April 7, 2020 were included. Some of them were excluded because they were duplicate or because the file was incomplete. A total of 279 tests were analyzed.

We performed correlation tests according to the prescriber (emergency departments versus outpatient wards), to the sampler (nurses, biologists, health care team in a medicalized nursing home), and to the laboratory.

3. Results

A total of 67 tests (24%) out of 279 were positive. The number of daily tests increased until March 30, reaching a peak of 32 tests performed, five of which were positive (Fig. 1). Overall, 20% of the tests were positive for women against 31% for men. The percentage of positive tests seemed to increase with age (30% for people aged over 81) (Table 1).

Outpatient prescriptions represented 191 tests, of which 42 (22%) were positive. Among those tests, 11 were performed by the Lafayette site, six of which were positive (55%). Emergency prescriptions accounted for 58 tests, of which 21 (36%) were positive.

The tests were significantly more frequently positive when prescribed within emergency departments than outpatient wards ($P = 0.04$). However, the type of sampler did not seem to have any impact on the test result ($P = 0.67$). Results of the various laboratories were of little significance ($P = 0.07$). However, it is interesting to compare the Lafayette site with other sites with less restrictive indications for tests. The tests were significantly more frequently positive when biologists applied a strict control of indications ($P = 0.02$).

4. Discussion

A peak seemed to have been reached around March 30. Chronological data seems to be similar to those of the Auvergne-Rhône-Alpes region [3]. Indeed, the epidemic follow-up indicators have been decreasing since the first weeks of April. The positivity rate (24 %) is close but higher than the region private laboratories positivity rate (20%).

COVID-19 can have several clinical forms: from pauci-symptomatic forms to feverish respiratory distress. Patients presenting with severe symptoms are more likely to have COVID-19 and thus to be tested positive. Time between symptom onset and performance of the test can also change the results [4]; the time-frame for test positivity therefore seems to be longer in patients presenting with severe forms [5].

We can assume that patients consulting at the emergency department have more severe clinical presentations. This could explain why the tests are significantly more frequently positive in the emergency departments than in outpatient wards. Unfortunately, we were not able to collect and analyze a sufficient amount of clinical data to support these assumptions. A further study including clinical data could clarify those results.

In the present study, the rate of positive tests tends to increase with age. As previously mentioned, the clinical form could explain this result as older people are more likely to be seriously affected