

Level of CRP predicts need for respiratory support in hospitalized COVID-19 patients

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Abstract

Purpose

Predictors of disease severity in COVID-19 are essential to identify patients requiring hospitalization. Our aim was to determine the relationship of C-reactive protein (CRP) with the need for respiratory support.

Methods

This was a retrospective monocentric study of all patients hospitalized for confirmed COVID-19 pneumonia. CRP was measured on admission in the serum. Patients were classified using the Pneumonia Severity Index (PSI) and a 3-stage internal severity score (ISS) based upon respiratory parameters. Chest CT scans performed on admission were analysed following guidelines. Correlations of CRP levels with disease severity, radiological score, oxygen or mechanical ventilation requirement, and death were studied.

Results

61 patients were included from March 13th to April 8th, 2020. CRP levels were better related to the ISS compared to the PSI, being 18 (5-54), 130 (50-147) and 169 (97-241) mg/L respectively for the low, intermediate and high severity groups ($p = 0.004$ and $p = 0.017$). Analysis of the 51 available CT scans found a smaller correlation between CRP levels and radiological score ($p < 0.05$). The CRP levels were related to oxygen requirement ($n = 50$, $p = 0.001$), mechanical ventilation ($n = 20$, $p = 0.004$) and death ($n = 10$, $p = 0.001$).

Conclusion

CRP level on admission was a good marker of clinical and radiological severity in COVID-19 pneumonia, and could be used to identify patients needing hospitalization and intensive care.

Introduction

The coronavirus disease 2019 (COVID-19) first appeared in Wuhan, China, in December 2019, then spread worldwide, with more than 4 million confirmed cases and 300 000 deaths as at 15 May 2020 [1]. It has rapidly become a major health public problem due to its high infectiousness [2].

Even though the vast majority of cases are mild, some patients will evolve to a severe respiratory illness, leading to lung failure and death [3]. Critical COVID-19 has a high mortality rate, reaching 26% in intensive care units (ICU) of Lombardy, Italy [4].

This pandemic has rapidly overwhelmed medical capacities, especially in ICU [5]. Risk stratification is therefore essential, and early effective predictors of disease severity and mortality are needed. Several studies have identified some risk factors for developing severe COVID-19 pneumonia, such as comorbid

conditions and older age [6]. Chest computed tomography (CT) scan has also been widely used in assessing COVID–19 pneumonia, and higher radiological score has been shown to be predictive of severe disease [7].

Others have found biological parameters to be predictors of mortality, such as D-dimers, troponin, proBNP and neutrophil-to-lymphocyte ratio [8]. As severe respiratory illness is characterized by a hyperinflammatory syndrome, two other studies have reported increased C-reactive protein (CRP) to be an independent risk factor for disease severity [9, 10].

We thus decided to investigate in this study the relationship between the CRP levels with clinical and radiological (chest CT) status on hospital admission, and its prognostic value on clinical outcomes such as respiratory support and death, in COVID–19 confirmed cases.

Methods

Ethical standard and study's population

It is a retrospective study conducted in the University Hospital of Guadeloupe (Pointe-à-Pitre, France), the reference hospital of the island for COVID–19. All adult patients (> 18 years old) hospitalized for COVID–19 pneumonia were included. The protocol was approved by the local ethical committee and patients included in the database “French COVID” (recorded center 050). Written informed consent was obtained from participants.

The definite diagnosis of COVID–19 pneumonia was established according to the case definition established by WHO interim guidance [11]. RNA detection of the SARS-CoV–2 was assessed by RT-PCR on respiratory secretion specimens (e.g. nasopharyngeal swab, endotracheal aspirate or bronchoalveolar lavage). Viral RNA was extracted using the Nucleospin Virus Macherey Nagel (Hoerd, France), and detection of SARS-CoV–2 RNA was obtained with a multiplexed PCR targeting two different regions of the RNA-dependent RNA polymerase (RdRp)-encoding gene (Eurogentec, Seraing, Belgium). Real-time RT-PCR was carried out with an Applied Bio System 7500 (Thermo Fisher Scientific, Courtaboeuf, France). Tests were considered positive when amplification was obtained with the two sets of primers.

Clinical data

All sociodemographic, clinical, laboratory and outcomes data were extracted from the medical files of the patients. Patients with simultaneous bacterial infection on admission were excluded, knowing that all patients had blood cultures, urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila*, and a respiratory sample in case of mechanical ventilation.

Clinical severity of patients on admission was categorized using the Pneumonia Severity Index (PSI) of Fine et al [12]. We also used an internal severity score (ISS) as described here: low severity group included

patients with PaO₂/FiO₂ > 350 mm Hg or no oxygen requirement or respiratory rate (RR) < 25/min, intermediate severity group included patients with PaO₂/FiO₂ 200–350 mm Hg or oxygen requirement ≤ 3L/min or RR 25–35/min, and high severity group included patients with PaO₂/FiO₂ < 200 mm Hg or oxygen requirement > 3 L/min or RR > 35/min or mechanical ventilation.

Ultrasensitive CRP levels were measured on serum in onsite laboratory, with immunoturbidimetry technique (Cobas 6000, Roche) and expressed in mg/L. Follow-up of CRP levels was based on individual medical decision, and we recorded all the values within the 7 first days of hospital admission, making sure no bacterial infection occurred during this period.

Chest CT analysis

Unenhanced spiral chest CT scan was performed on hospital admission and analyzed independently by three experienced radiologists; when there was a discrepancy, the final result was reached by consensus. Image readers were not aware of the patients clinical and biological characteristics. The CT scan analysis was performed respecting the guidelines of the French Society of Thoracic Imaging [13]. A CT score was used to measure the extent of lung involvement according to the following criteria: score 0 (no involvement), score 1 (1–10%: minimal involvement), score 2 (11–25%: moderate involvement), score 3 (26–50%: important involvement), score 4 (51–75%: severe involvement) and score 5 (76–100%: critical involvement).

Clinical outcomes

The outcomes studied for the prognostic value of CRP level on admission were oxygen requirement, transfer to ICU, need for mechanical ventilation, length of stay and death. Days were calculated until date of death for deceased patients.

Statistical analysis

Continuous variables are expressed in median [95% IQR]. Categorical variables are expressed as counts and percentages. The univariate analysis was performed using a t-student test, groups were compared using Fisher exact test, Mann-Whitney test and Kruskal-Wallis's test as required. A value of $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using Statview© version 5.0 software.

Results

Patients characteristics

A total of 63 patients admitted to our hospital between March 13th and April 08th, 2020, were included; 2 patients were excluded because of simultaneous bacterial pneumonia present on admission.

The demographic, clinical, radiological and biological characteristics of patients are summarized in Table 1. Median age was 65 years (interquartile range [IQR] 57–76 years), with 56% (34/61) of males. At least 1 comorbidity was present in 80% (49/61) of patients, with majority of hypertension (56%) and diabetes (43%). The median delay between symptom onset and admission to hospital was 8 days (IQR, 5–12 days).

The PSI score was 1 or 2 for 24 patients (39%), 3 for 10 patients (16%), and 4 or 5 for 27 patients (44%). Regarding the ISS, patients were mostly in the high severity group (28/61, 46%).

CT scans were realized in 51 patients: 19 (37%) patients with scores 0–2, 15 (29%) in score 3, 17 (33%) in scores 4 or 5.

Median CRP level on admission was 108 mg/L (IQR, 48–174 mg/L).

Clinical outcomes

Oxygen therapy has been used for at least one day in 82% (50/61) of patients, with a median duration of 9 days. Moreover, 30 (49%) patients required ICU admission: 17 (28%) were directly admitted in ICU, whereas 13 (21%) were transferred secondarily from a medical ward with a majority (11/13) being transferred during the first week of their hospital stay.

Finally, 20 (33%) patients needed mechanical ventilation, and 10 (16%) died. Median length of hospital stay (LOS) was 10 days (IQR, 6–16 days).

Of the 51 survivors, 49 patients were discharged. One patient was still in ICU but without invasive ventilation, and one patient was still in a medical ward without oxygen requirement.

Correlation of CRP with clinical and radiological severity on admission

Using the PSI while grouping the 5 risk classes into 3 (classes 1–2, 3 and 4–5), there was no statistical difference for CRP levels between these 3 groups ($p = 0.212$ and $p = 0.104$, see Figure 1A). Using the ISS, median (IQR) CRP levels were significantly different with respectively 18 (5–54), 130 (50–147) and 169 (97–241) mg/L in the low, intermediate and high severity groups. ($p = 0.004$ and $p = 0.017$, see Figure 1A).

Similarly, radiological score, while grouping the 6 scores into 3 categories ($\leq 25\%$, 26–50% and $> 50\%$ lung involvement), was also related to the level of CRP ($p = 0.032$ and $p = 0.049$, see Figure 1A).

Correlation of CRP on admission with respiratory support and death

As illustrated in Figure 1B, CRP levels on admission were significantly higher in patients requiring oxygen therapy ($p = 0.0001$) and in patients requiring mechanical ventilation ($p = 0,0004$) at any moment during their hospital stay, compared to patients not needing these supports. CRP was also significantly higher ($p = 0.0013$) in non-survivors compared to survivors. Using a cut-off of 100 mg/L, obtaining 2 groups of 28 and 33 patients, all those having a CRP value on admission > 100 mg/L (33/33) will need oxygen therapy at some point. Furthermore, all the patients who died were in this group (10/33, 30%), while no deaths occurred in patients having a CRP level on admission < 100 mg/L.

Finally, as we can see on Figure 1B, the kinetics of CRP during the 7 first days of hospitalization were clearly different between ventilated patients showing increasing levels of CRP and non-ventilated patients showing decreasing levels, with a significant difference at each time-point.

Discussion

In this study, we found that CRP levels on admission of patients hospitalized with COVID-19 pneumonia were strongly related to clinical severity, when using the ISS, but not to the PSI. We also showed that CRP was correlated with radiological score of chest CT scans done on admission. Finally, it was also strongly associated with respiratory support such as oxygen requirement and need for mechanical ventilation, and ultimately to death.

Our study has some limitations. It is a retrospective study of a small cohort of patients included during the COVID-19 epidemic peak on our territory. Nevertheless, distribution of patients in the different clinical severity categories was quite well balanced.

Prognostic tools to predict progression to severe forms are essential in clinical practice when facing a new epidemic disease such as COVID-19 because of its unpredictable clinical course and the risk of overwhelming medical capacity. To date, mainly clinical risk factors for complications of COVID-19 have been identified [14].

We found that CRP on admission was correlated with clinical severity, using our internal severity score which has 3 categories defined by practical respiratory criteria. This association was not found using the PSI: this can probably be explained by the fact that this score has been initially designed for evaluating community-acquired pneumonia mainly represented by bacterial pneumonia. Indeed, our ISS is presumably more suitable for a viral disease like COVID-19.

Chest CT scan has been widely performed in assessing COVID-19 pneumonia. It has been used as a diagnostic tool [15], but also as a marker of severity since chest CT score has been correlated with mortality [16]. To our knowledge, except one study that correlated CRP levels and the diameter of the largest lung lesion [17], relation between CRP and lung involvement severity on chest CT scan has not

been previously reported. As we found that CRP values were significantly associated with the CT score and clinical severity, CRP measurements could be used as an alternative tool to chest CT for evaluating the severity of the pulmonary disease, particularly if chest CT is not feasible.

Several laboratory parameters associated with a severe evolution have been identified in COVID-19 [8]. Herold et al. [18] recently found higher levels of interleukin-6 in serum of patients needing mechanical ventilation, but its measure is not as available as CRP, a well-known non-specific acute-phase protein induced by IL-6 in the liver [19]. And higher CRP values in severe cases have been reported [10] suggesting that CRP reflects the inflammatory state of the pulmonary disease. Similarly, Ruan et al. [20] found higher CRP levels in patients who died compared to discharged patients. This could be explained by the fact that CRP is not just a marker of inflammation or infection but also an important regulator of inflammatory processes [21].

Moreover, we showed that CRP levels were associated with respiratory support such as oxygen requirement and need for mechanical ventilation, and ultimately with death. Also, the CRP kinetics during the first week of hospitalization was clearly different depending if patients required or not mechanical ventilation. Finally, we found a cut-off value of 100 mg/L above which all patients would need to be hospitalized at some point for oxygen therapy, and under which no deaths occurred. Thus, CRP could be an effective marker to predict upcoming respiratory failure and therefore help for correct allocation of patients at an early stage.

Otherwise, even though no treatment has so far been proven to be effective [22], some small studies have reported promising results with the anti-IL6 tocilizumab [23,24]. As CRP appears as an easy tool to evaluate severity and inflammation status in COVID-19, this biomarker could be used to select patients that would benefit from that specific treatment.

Finally, as it has been done with chest CT scans [25], the potential contribution of CRP follow-up in COVID-19 management should be explored, ideally in a prospective way.

In conclusions, we found that CRP level on admission in COVID-19 pneumonia is strongly correlated to clinical and radiological severity, need for respiratory support and death. It might therefore be an easy and cheap tool for correct triage of patients needing hospitalization or intensive care admission.

Declarations

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Conflicts of interest

The authors declare no conflict of interest.

Availability of data and material (data transparency): not applicable

Code availability: not applicable

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Table

Table 1: Characteristics of 61 patients hospitalized with COVID-19 pneumonia, according to internal clinical severity group.

Characteristic s	Low severity n = 16 (26%)	Intermediate n = 17 (28%)	High severity n = 28 (46%)	P	Total n = 61 (100%)
Age (years)*	58 [52-66]	65 [57-71]	69 [63-77]	0.074	65 [57-76]
Sex-ratio (M/F)	0.77	0.88	2.11	0.210	1.26
Underlying conditions	13 (81)	10 (59)	26 (93)	0.022	49(80)
At least one comorbid condition	6 (37)	5 (29)	15 (54)	0.215	26 (43)
	10 (62)	6 (35)	18 (64)	0.134	34 (56)
Diabetes	1 (6)	0	4 (14)	0.225	5 (8)
Hypertension	1 (6)	4 (24)	2 (7)	0.219	7 (11)
Cardiopathy	9 [5-10]	8 [8-14]	8 [4-13]	0.467	8 [5-12]
Other comorbid conditions	11	14	26		51
	9 (82)	8 (57)	2 (8)	< 0.001	19 (37)
Duration of symptoms before admission*	2 (18)	5 (36)	8 (31)	0.621	15 (29)
	0	1 (7)	16 (61)	< 0.001	17 (33)
Chest CT scan on admission (n = 51)	18 [5-54]	130 [50-147]	169 [97-241]	< 0.001	108 [48-174]
	2 (12)	10 (59)	21 (75)	< 0.001	33 (54)
Lung affected ≤ 25%	6.45 [5.70- 7.62]	6.30 [5-7.80]	6.90 [5.07- 8.85]	0.704	6.60 [5.10- 8.50]
	4.21 [2.63- 4.97]	4.43 [3.25- 5.83]	5.58 [4.38- 7.28]	0.016	4.74 [3.85- 6.31]
Lung affected 26- 50%	1.34 [1.11- 1.67]	1.24 [0.95- 1.85]	1.02 [0.54- 1.22]	0.008	1.15 [0.81- 1.47]
Lung affected > 50%				< 0.001	
	6 (37)	12 (71)	26 (93)	0.037	44 (72)
Biological data on admission		2 (12)	10 (36)	< 0.001	13 (21)
	1 (6)	17 (100)	28 (100)	< 0.001	50 (82)
<i>C-reactive protein (mg/L)*</i>	5 (31)	4 (24)	25 (89)	< 0.001	30 (49)
	1 (6)	1 (6)	19 (68)	< 0.001	20 (33)
C-reactive protein ≥ 100 mg / L	0	8 [6-12]	16 [10-29]	0.0083	10 [6-16]
	4 [2-8]	0			

Leucocytes (x10 ³ /μL)*	0	10 (36)	10 (16)
Polymorphonuclear (x10 ³ /μL)*			
Lymphocytes (x10 ³ /μL)*			
Treatment			
Hydroxychloroquine + azithromycin			
Glucocorticoids			
Oxygen therapy			
Intensive care admission			
Mechanical ventilation			
Length of hospital stay*			
Deaths			

Values are expressed in n (%), or median [IQR]*.

Figures

