Early evolution of biochemical markers in severe and non-severe patients infected with COVID-19

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INTRODUCTION

Long-term In December 2019, a cluster of severe unexplained pneumonia was identified in the city of Wuhan, in China [1]. This was caused by a novel Coronavirus species called SARS-CoV-2 [2]. The World Health Organization (WHO) assigned in February 2020 the name COVID-19 to designate the disease caused by this virus. COVID-19 may be asymptomatic which amplifies viral spread [3]. However, common clinical symptoms include dry cough, fever, and fatigue [4]. Less common symptoms include headache, abdominal pain, nausea, vomiting, anosmia, and dysgeusia [4,5]. The severe forms of COVID-19 are similar to those of acute respiratory syndrome (SARS). World Health Organization's (WHO) guidelines define “severe disease” as adults with pneumonia associated with one of the following conditions: respiratory rate >30 breaths/ min; severe respiratory distress; or oxygen saturation (SpO2) ≤ 90% on room air [6]. In this study we describe biochemical disturbances of SARS-CoV-2 infection in a sample of patients that may correlate with COVID-19 disease severity.

PATIENTS AND METHODS

To this is a prospective comparative study including adult patients with COVID-19 disease hospitalized in Avicenna military hospital, Marrakech from 1* February to 31st May 2021. The inclusion criteria for enrollment into the study were: positive real-time polymerase chain reaction (RT-PCR) from naso-pharyngeal swab specimens, age ≥ 18 years, complete clinical data. The clinical pneumonia severity was defined as suggested in the literature [6,7]. The study was sponsored by the faculty of Medicine and Pharmacy of Marrakech (Cadi Ayyad University), approved by ethic commission of Avicenna military hospital, and complied with the Declaration of Helsinki. During the study period 70 Non-vaccinated COVID-19 patients were hospitalized at the Avicenna military hospital, 50 patients in the COVID-19 isolation hospital (non-severe group) and 20 patients in the medical intensive care unit (severe group). All blood samples were obtained at the admission, at 24-48 hours, 48-72 hours, and 72-96 hours on a dry tube, centrifuged at 3000 rpm for five minutes. The determination of biochemical parameters was performed on the Cobas Roche® multiparametric analyzer.

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Word count: 1597 Tables: 0 Figures: 00 References: 34

Received: 27 February, 2021, Manuscript No. ipaom-21-12407; Editor Assigned: 05 March, 2022, Pre QC No. P-12407; QC No. Q-7477; Reviewed: 17 March, 2022, Revised: 22 March, 2022, Manuscript No. R-12407; Published: 31 March, 2022.
All of the 70 patients underwent a screening of biochemical indexes: Inflammatory Biomarkers (Procalcitonin, CRP, ferritinemia) Cardiac markers (High-Sensitivity Troponin T(us), NT-proBNP), renal function tests (Blood urea nitrogen, creatinine), liver Function tests (AST, ALT, LDH, albumin), pro-inflammatory cytokine (Interleukine-6).

**Statistical analysis**

Statistical analysis was performed on IBM SPSS Statistics V25, latest version. Quantitative variables are expressed as median and mean and Fisher’s test was used for analysis of qualitative variables. Pearson correlation analysis was used to analyze the relationship between different biochemical parameters and severity/outcome of COVID-19. A P-value <0.05 was considered statistically significant.

**RESULTS**

**Epidemiology**

Overall, 70 COVID-19 patients were admitted at our hospital, 20 patients (severe group) in the medical intensive care unit and 50 patients (non-severe group) in the COVID-19 stable unit. Their ages ranged from 30 to 94 years; the median patient age was 59 years (64 years on severe group versus 58 years on non-severe group). 84% of patients were male. The median diagnostic delay was 9 days on severe group and 6 days on non-severe group. The main comorbidities were diabetes (18%), diabetes associated to arterial hypertension (10%), arterial hypertension (8%) and nephropathies (7%).

**Biochemical alterations**

We compared the biochemical abnormalities between the 2 study groups as listed in Tab.1.

**Inflammation markers**

C-reactive protein (CRP) increased in 75% first day [median 141.2 mg/L vs. 84.2 mg/L, p = 0.2], 94% second day [median 135.5 mg/L vs. 38.2 mg/L, p = 0.03], then 28% third day [median 148.4 mg/L vs. 27.6 mg/L, p = 0.01]. Procalcitonin (PCT) increased in 25% first day [median 1.9 ng/mL vs. 0.58 ng/mL, p = 0.1], 30% second day [median 6.0 ng/ml vs. 0.33 ng/mL, p = 0.08], then 18% third day [median 5.55 ng/mL vs. 0.12 ng/mL, p = 0.01]. Hyperferritnemia was noticed in 57% first day [median 1069.8 ng/ml vs. 507.1 ng/ml, p = 0.01], 58% second day [median 993.7 ng/ml vs. 520.3 ng/ml, p = 0.01].

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Tab. 1. We compared the biochemical abnormalities between the 2 study groups as listed in.

| Paramètre                  | Reference Values | Total       | Moderee (n=50) | Severe (n=20) | P  |
|----------------------------|------------------|-------------|----------------|---------------|----|
| Procalcitonin (day 1)      | 0.5 ng/mL        | 18 (25%)    | 7 (14%)        | 11 (55%)      | 0.1|
| Procalcitonin (day 2)      |                  | 21 (30%)    | 5 (10%)        | 16 (80%)      | 0.08|
| Procalcitonin (day 3)      |                  | 13 (18%)    | 0 (0%)         | 13 (65%)      | 0.01|
| CRP (day 1)                | <5 mg/L          | 53 (75%)    | 35 (70%)       | 18 (90%)      | 0.2|
| CRP (day 2)                |                  | 66 (94%)    | 46 (92%)       | 20 (100%)     | 0.03|
| CRP (day 3)                |                  | 20 (28%)    | 8 (16%)        | 12 (60%)      | 0.01|
| Hyperferritinemia (day 1)  | 30-400 ng/mL     | 40 (57%)    | 26 (52%)       | 14 (70%)      | 0.01|
| Hyperferritinemia (day 2)  |                  | 41 (58%)    | 27 (54%)       | 14 (70%)      | 0.04|
| Interleukin-6 (day 2)      | 13 pg/mL         | 66 (94%)    | 46 (92%)       | 20 (100%)     | 0.03|
| High-sensitivity troponin T (day 1) | <0.014 mg/L | 4 (5%) | 0 (0%) | 4 (20%) | <0.01 |
| High-sensitivity troponin T (day 2) |              | 3 (4%) | 0 (0%) | 3 (15%) | 0.08 |
| NT-Pro-BNP (day 1)         | <125 pg/mL       | 3 (4%)      | 1 (2%)         | 2 (10%)       | <0.01|
| Blood urea nitrogen (day 1) | 2.50-7.50 mmol/L | 23 (32%) | 11 (22%) | 12 (60%) | <0.01 |
| Blood urea nitrogen (day 2) |                  | 32 (45%) | 16 (32%) | 16 (80%) | <0.01 |
| Creatinine (day 1)         | 60-120 μmol/L    | 16 (22%)    | 8 (16%)        | 8 (40%)       | 0.2 |
| Creatinine (day 2)         |                  | 17 (24%)    | 5 (10%)        | 12 (60%)      | 0.05|
| Albumin (day 1)            | 35-50 g/L        | 9 (13%)     | 1 (2%)         | 8 (40%)       | 0.01|
| Albumin (day 2)            |                  | 15 (21%)    | 4 (2%)         | 11 (55%)      | <0.01|
| ALT (day 1)                | < 65 U/L         | 11 (15%)    | 6 (12%)        | 5 (25%)       | 0.09|
| ALT (day 2)                |                  | 9 (13%)     | 6 (12%)        | 3 (15%)       | 0.1 |
| AST (day 1)                | < 50 U/L         | 17 (24%)    | 9 (18%)        | 8 (40%)       | 0.07|
| AST (day 2)                |                  | 6 (8%)      | 4 (8%)         | 2 (10%)       | 0.1 |
| LDH (day 1)                | 135-225 U/L      | 55 (78%)    | 35 (70%)       | 20 (100%)     | 0.06|
| LDH (day 2)                |                  | 58 (82%)    | 38 (76%)       | 20 (100%)     | 0.08|
Liver function

ALT increased in 15% first day [median 102 U/L vs. 45 U/L, p= 0.09] 13% second day [median 52 U/L vs. 34 U/L, p= 0.1]. The increase in AST in 24% first day [median 29 U/L vs. 33 U/L, p= 0.07], 8% second day [median 156.5 U/L vs. 86.9 U/L, p= 0.1]. LDH increased in 78% first day [median 420 U/L vs. 21% second day [median 527 U/L vs. 415 U/L, p= 0.08]

Renal function

Blood Urea nitrogen increased in 32% first day [median 18.2 mmol/L vs. 8.2 mmol/L, p<0.01], 45% second day [median 17.4 mmol/L vs. 8.7 mmol/L, p<0.01]. The increase increatinine in 22% first day [median 144.1 μmol/L vs. 117.5 μmol/L, p= 0.2], 24% second day [median 156.5 μmol/L vs. 86.9 μmol/L, p= 0.05]. Hypoalbuminemia in 13% first day [median 30.7 g/L vs. 32.3 g/L, p= 0.01], 21% second day [median 27.8 g/L vs. 31.6 g/L, p<0.01]

DISCUSSION

The aim of our study was to compare the early biochemical disturbances associated to COVID-19 between severe and non-severe patients, and to report the correlation between these disturbances and the clinical form of the disease. Diabetes and arterial hypertension were the main comorbidities noted in our study, especially in the severe group. These results match most of studies, relating higher morbidity and mortality among patient with comorbidities [8-12]. Overall, inflammation markers titles increased differently between the two study groups. In fact, Ferretinemia increase was the most significant at the admission (P= 0.01), Interleukin-6 and CRP the second day (P= 0.03), then Procalcitonin and CRP the third day (P= 0.01). Hyperferritinemia is a part of the innate immune response, lymphocyte function modulator that can be used for monitoring inflammation [13,14] and associated to Interleukin-6 as a key markers of macrophage activation syndrome in severe COVID-19, potentially implicating it in a pro-inflammatory and prothrombotic syndrome [15,16]. Interleukin-6 is a pro inflammatory cytokine associated with negative clinical outcomes and significantly elevated in complicated COVID-19 patients [17]. CRP is a good predictor of inflammation outcomes in different tissues, and being also a good screening tool for severity in initial phase of COVID-19 [18,19]. Procalcitonin titles tends to be close to normal range on non-severe patients, a significant increase may reflects bacterial co-infection or evolution to a severe form [20,21]. In our study, increased ALT, AST and LDH levels especially at the admission were significantly associated to severe forms of COVID-19. Studies showed that liver markers increase was suggestive of evolution to severe forms and bad outcomes [22-24]. Abnormal titles of High-sensitivity troponin and NT-Pro-BNP, especially at the admission, was highly correlated to severe forms and leading to fatal outcome. High titles of troponin is mainly directly linked to myocardial infarction, and indirectly to systemic arterial embolism [25-28]. NT-pro-BNP titles of severe COVID-19 patients at admission, may be an excellent risk factor of poor prognoses or in hospital death [29]. The blood urea nitrogen, creatinine and albumin abnormalities are excellent predictive tools for COVID-19 severity and possible kidney damage [30-32]. Besides, concentrations of amylase, lipase, lactic acid and plasma angiotensin II may be suggestive of the evolution of COVID-19 severity [32]. In addition, HDL-Cholesterol and serum potassium concentrations were negatively correlated with the severity of the disease [34]. In fact, HDL-Cholesterol is known to be a protective factor in a plenty of COVID-19 forms, including the pneumonia.

CONCLUSION

Procalcitonin, CRP, Ferretinemia, High-sensitivity troponin, NT-Pro-BNP, blood urea nitrogen, creatinine, albumin and LDH are very good predictive tools of severity of COVID-19, especially in the first 72 Hours. A close supervision and adapted biochemical parameters screening are vital for patients, especially those with comorbidities, more at risk to develop a severe form with bad outcome.

CONFLICTS OF INTEREST

The authors declare no competing interests.

All authors declare that the material has not been published elsewhere, or has not been submitted to another publisher.

DATA AVAILABILITY

Authors declare that all related data are available concerning researchers by the corresponding author’s email.

ACKNOWLEDGMENTS

None.
