Archives of Medicine©
14 (3) 2022 : 001-004 • RESEARCH ARTICLE

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

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SUMMARY

Generally, Coronavirus disease 2019 (COVID-19) is an emerging infection that has caused a pandemic, it is due to a virus of the coronavirus family called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which can evolve into severe forms leading to death. Several biochemical alterations have been described in COVID-19 patients with great significance for clinical diagnosis and outcome prediction. The aim of this study is to compare early evolution of biochemical disturbances in COVID-19 patients and correlate them to severity of the disease. This study was conducted in 70 COVID-19 patients hospitalized at the Avicenna military hospital. 20 patients in the medical intensive care unit (severe group) and 50 patients in the COVID-19 isolation hospital (non-severe group). Across our laboratory data analysis of the two groups of COVID-19 patients, we demonstrated that high titles and early elevation of ferretinemia, Interleukin-6, High-Sensitivity Troponin T (us), NT-Pro-BNP, Blood Urea nitrogen, Creatinine and LDH are significantly correlated to severity of the disease.

The analysis of this study through the recent scientific literature demonstrates the interest of early monitoring of biochemical markers in the diagnosis of severity and monitoring of severe forms of COVID-19

Keywords: Prognosis; Early evolution; COVID-19; Laboratory data

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Word count: 1597 **Tables:** 01 **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.

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 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 1st February to 31th May 2021. The inclusion criteria for enrollment into the study were: positive real-time polymerase chain reaction (RT-PCR) fromnaso-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.

All of the 70 patients underwent a screening of biochemical indexs: 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 =

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
Hyperferritinemia (day 3)		31 (44%)	17 (34%)	14 (70%)	0.1
Interleukin-6 (day 2)	13 pg/mL	66 (94%)	46 (92%)	20 (100%)	0.03
High-sensitivity troponin T (day 1)	<0.014 ng/mL	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

0.04], then 44% third day [median 1147.7 ng/ml *vs.* 660.6 ng/mL, p = 0.1]. Interleukin-6 (IL-6) was screened second day and we found increased titles in 94% [median 969.4 pg/mL *vs.* 87.0 pg/mL, p = 0.03].

Cardiac markers

High-Sensitivity Troponin T testing was positive in 5% first day (p<0.01), 4% the second day (p= 0.08), all patients were from the severe group. Pro-Brain Natriuretic Peptide (NT-Pro-BNP) measured the first day, was increased in 4% (2 patients from severe group *vs.* 1 from non-severe group p< 0.01).

Renal function

Blood Urea nitrogen increased in 32% first day [median 18.2mmol/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]

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 inAST in 24% first day [median 29U/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% firs t day [median 583 U/L *vs.* 420 U/L, p= 0.06], 82% second day [median 527 U/L *vs.* 415 U/L, p= 0.08]

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 matches 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 prothromboticsyndrome [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 ofHigh-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 myocadial infraction, 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 [30,33]. 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.

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