Journal of Acute Disease

Original Article

doi: 10.4103/2221-6189.355311 jadweb.org

Different routine laboratory tests in assessment of COVID−19: A case−control study

Imene Adouani[1,2✉], Tassaadit Bendaoud[1,3], Hadjer Belaaliat[1,3], Wahiba Teniou[1,3], Faiza Keriou[1,4], Farida Djabi[1,2,3]

[1]*Faculty of Medicine, University Ferhat Abbas Setif−1, Setif, Algeria*

[2]*Laboratory of Biotechnology and Genomics in Medical Sciences, Setif, Algeria*

[3]*Central Laboratory, Setif Hospital, Setif, Algeria*

[4]*Unit of Pneumology, Setif Hospital, Setif, Algeria*

ABSTRACT

Objective: To identify helpful laboratory paprameters for the diagnosis and prognosis of COVID-19.

Methods: An observational retrospective study was conducted to analyze the biological profile of COVID-19 patients hospitalized in the Unit of Pulmonology at Setif hospital between January and December 2021. Patients were divided into two groups: the infection group and the control group with patients admitted for other pathologies. The infected group was further divided according to the course of the disease into non-severe and severe subgroups. Clinical and laboratory parameters and outcomes of admitted patients were collected.

Results: The infection group included 293 patients, of whom 237 were in the non-severe subgroup and 56 in the severe subgroup. The control group included 88 patients. The results showed higher white blood cells, neutrophils, blood glucose, urea, creatinine, transaminases, triglycerides, C-reactive protein, lactate dehydrogenase, and lower levels of lymphocyte, monocyte and platelet counts, serum sodium concentration, and albumin. According to ROC curves, urea, alanine aminotransferase, C-reactive protein, and albumin were effective diagnosis indices on admission while neutrophil, lymphocyte, monocyte, glycemia, aspartate aminotransferase, and lactate dehydrogenase were effective during follow-up.

Conclusions: Some biological parameters such as neutrophil, lymphocyte, monocyte, glycemia, aspartate aminotransferase, and lactate dehydrogenase are useful for the diagnosis of COVID-19.

KEYWORDS: Algeria; Alteration; Biological parameters; COVID-19; Pneumology

1. Introduction

COVID-19 out-brake in Algeria began in March 2020. A considerable number of infected subjects remain asymptomatic, while symptomatic cases have different symptoms ranging from minimal nonspecific symptoms to acute respiratory distress syndrome with various complications and high mortality[1-6]. It might be a challenge to diagnose and manage the infection and its complications. Laboratory parameters might be important to confirm the diagnosis, determine its severity, monitor the treatment, and

Significance

The present study analyzed different laboratory tests of Algerian COVID-19 patients. It shows that urea, alanine aminotransferase, C-reactive protein, and albumin were interesting on admission while neutrophil, lymphocyte, monocyte, glycemia, aspartate aminotransferase, and lactate dehydrogenase were more performing during follow-up. The study added additional important information to the existing literature on COVID-19.

✉To whom correspondence may be addressed. E-mail: i.adouani@univ-setif.dz

How to cite this article: Adouani I, Bendaoud T, Belaaliat H, Teniou W, Keriou F, Djabi F. Different routine laboratory tests in assessment of COVID-19: A case-control study. J Acute Dis 2022; 11(4): 140-149.

Article history: Received June 18, 2022; Revision July 22, 2022; Accepted August 10, 2022; Available online 6 September, 2022

reduce mortality[7,8]. There is a lack of data analyzing the different routine biological parameters in an Algerian population up to now, our study aims to screen these laboratory parameters related to COVID-19.

2. Patients and methods

2.1. Study setting

A case-control study was conducted on patients recruited from the Unit of Pneumology of the University Hospital of Setif from January to December 2021.

2.2. Ethical statement

This study was conducted following the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Ferhat Abbas Setif-1 on November 2021 (SC11-2021). The informed patient consent was waived by obtaining approval from the Ethics and Scientific Committees of the University of Ferhat Abbas Setif-1 due to the retrospective nature.

2.3. Inclusion and exclusion criteria

All patients admitted to the Unit of Pneumology from January to December 2021 were included. Patients with incomplete medical and/or biological records were excluded. The included patients were stratified into the infection group of patients diagnosed with COVID-19 using clinical symptoms and/or chest computed tomography (chest-CT) at admission and the control group with patients hospitalized for other pathologies. The infection group was further classified into non-severe and severe subgroups based on the outcomes (discharge from the hospital, transfer to other units, or death).

2.4. Primary outcomes

Data on demographic characteristics, underlying comorbidities, clinical characteristics, and para-clinical findings, including radiological and laboratory tests, were collected from paper medical records. Hospitalization time, hospital discharge time, and time from disease onset to hospitalization were also noted.

2.5. Statistical analysis

Epitools® online calculator has been used to estimate the sample size needed for our case-control study (P=0.04, power=80%, confidence level=95%, assumed odds ratio=5). A minimum of 82 patients were needed in each group.

IBM® SPSS 26.0 was used for data analysis. Categorical variables were presented as absolute numbers and percentages, while continuous variables were presented as mean±SD or median (Q1, Q3). Student-t test or Mann-Whitney U test were used to compare continuous variables. Chi-square or Fisher's exact tests were used to compare categorical variables. Odds ratios (ORs) were used to explore the association between different laboratory test abnormalities and the severity of infection. Receiver Operating Characteristic (ROC) curves were used to test the effectiveness of the studied parameters for COVID-19 diagnosis and prognosis.

3. Results

A total of 434 patients were admitted to the pneumology unit from January to December 2021. Incomplete medical and/or biological records led to the exclusion of 53 cases. The infection group comprised 293 COVID-19 patients while the control group included 88 non-COVID-19 patients (Figure 1). Among COVID-19 patients, there were 56 (19.1%) severe patients while the non-severe group included 237 (80.9%) patients. A total of 40 (13.6%) patients died and 16 (5.4%) were transferred to other units such as Intensive Care Unit, Internal Medicine Department, Infectious Diseases Department, and 56 non-severe patients were discharged from the hospital.

3.1. Socio–economic and demographic characteristics

The age ranged from 16 to 103 years. The median age (Q1, Q3) in the infection group, control group, non-severe, and severe groups were 66 (53, 74), 55 (36, 70), 64 (52, 73), and 72 (60, 78) years. The sex ratio in the infection group, control, non-severe and severe groups were 2.02, 3.00, 1.82, and 3.31 with male predominance. Most patients lived in Setif, were married, employed, and had a medium socioeconomic level.

Only age and socioeconomic level showed significant differences among all groups. Infected patients and severe cases were older. Furthermore, there were more patients with good socioeconomic levels in the infection group (Tables 1&2).

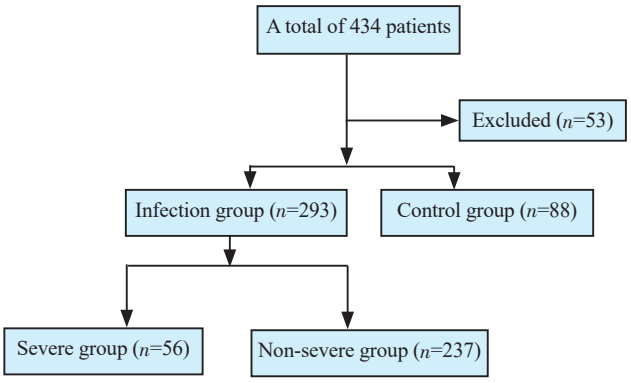

Figure 1. The study flowchart.

3.2. Comorbidities

In the infection group, comorbidities were observed in 76.8% of patients, and these were represented predominantly by arterial hypertension (41.3%), benign prostatic hyperplasia (36.2%), diabetes (31.7%), respiratory diseases (25.3%), heart disease (9.2%), dysthyroidism (5.8%), and anterior COVID-19 (2.7%). Comorbidities were present in 74.3% of non-severe and 87.5% of the severe subgroups. Among the control cases, 62.2% had comorbidities including respiratory diseases (33%), arterial hypertension (19.3%), diabetes (13.9%), and anterior COVID-19 (13.6%) (Tables 1&2).

Patients with comorbidities (*OR*: 1.98, 95% *CI*: 1.19-3.30, *P*=0.008) and medication history (*OR*: 1.80, 95% *CI*: 1.06-3.04, *P*=0.027) were more in infection group than the control group, particularly among severe cases (*P*=0.035 and *P*=0.01, respectively) (Tables 1&2). There were more subjects without unhealthy habits (*OR*: 2.21, 95% *CI*: 1.35-3.60, *P*<0.05) in the infection group than the control group. More patients in the control group [35 (11.9%)] were active smokers compared to the infection patients [29 (33.0%)]. Furthermore, more patients who were in contact with suspected or confirmed COVID-19 subjects were in the infection group (*OR*: 11.63, 95% *CI*: 4.61-29.41, *P*<0.05), but the difference was not significant between the severe and non-severe groups.

Table 1. Socio-economic and demographic characteristics and physical signs of control group and infection group (*n*=381).

Items	Control group, *n*=88	Infection group, *n*=293	χ^2/t	*P*
Sex, *n*, %				
Male, *n*=262	66 (75.0%)	196 (66.9%)	2.07	0.150
Female, *n*=119	22 (25.0%)	97 (33.1%)		
Age, years, median (Q1, Q3)	55 (36, 70)	66 (53, 74)	8534.00	0.001
Socioeconomic level, *n*, %				
Low, *n*=14	6 (6.8%)	8 (2.7%)	3.20	0.077
Medium, *n*=321	75 (85.2%)	246 (84.0%)	0.08	0.775
Good, *n*=28	2 (2.3%)	26 (8.9%)	4.33	0.037
Non-mentioned, *n*=18	5 (5.7%)	13 (4.4%)	/	/
Marital status, *n*, %				
Single, *n*=27	21 (23.9%)	6 (2.0%)	48.92	<0.001
Married, *n*=306	59 (67.0%)	247 (84.3%)	12.74	<0.001
Widowed, *n*=37	3 (3.4%)	34 (11.6%)	5.18	0.023
Non-mentioned, *n*=11	5 (5.7%)	6 (2.0%)	/	/
Employment, *n*, %				
Yes, *n*=284	69 (78.4%)	215 (73.4%)	0.90	0.342
No, *n*=97	19 (21.6%)	78 (26.6%)		
Unhealthy habits, *n*, %				
None, *n*=200	33 (37.5%)	167 (57.0%)	10.32	0.001
Active smoking, *n*=64	29 (33.0%)	35 (11.9%)	21.37	<0.001
Ex-smoker, *n*=107	21 (23.9%)	86 (29.4%)	1.01	0.315
Traditional combustion, *n*=42	7 (7.9%)	35 (11.9%)	1.01	0.295
Alcoholism, *n*=6	2 (2.3%)	4 (1.4%)	0.36	0.421
Medication history, *n*, %				
Yes, *n*=142	24 (27.3%)	118 (40.3%)	4.89	0.027
No, *n*=65	21 (23.9%)	44 (15.0%)		
Non-mentioned, *n*=174	43 (48.9%)	131 (44.7%)	/	/
Comorbidities, *n*, %				
Yes, *n*=280	55 (62.2%)	225 (76.8%)	7.10	0.008
No, *n*=101	33 (37.5%)	68 (23.2%)		
In contact with suspected or confirmed COVID–19 subjects, *n*, %				
Yes, *n*=126	5 (5.7%)	121 (41.30%)	38.78	<0.001
No, *n*=255	83 (94.3%)	172 (58.7%)		
Time between the onset of symptoms and hospitalization, d, median (Q1, Q3)	4 (1, 9)	7 (7, 10)	6517.50	0.001
Respiratory rate, cycles/minute, median (Q1, Q3)	23 (22, 25)	25 (22, 27)	2790.50	0.001
Partial oxygen saturation (SpO_2), %, median (Q1, Q3)	94 (87, 96)	85 (78, 89)	16483.50	0.001
Mean heart rate, bpm, mean±SD	94.82±15.61	97.43±14.51	5056.00	0.186
Weight, kg, mean±SD	67.65±15.83	81.81±15.45	483.50	<0.001

Active smoker: regular smoking with at least one cigarette per day; Ex-smoker: smokers who had quit smoking for more than five years; Traditional combustion: the use of wood or oil heater; Alcoholism: the consumption of alcoholic drinks; Medication history: different medications that the patients were under such as antihypertensive, antidiabetic, *etc*.

Table 2. Socio-economic and demographic characteristics and physical signs of severe group and non-severe group (n=293).

Items	Non–severe group, n=237	Severe group, n=56	χ^2/t	P
Sex, *n*, %				
Male, n=196	153 (64.6%)	43 (76.8%)	3.06	0.080
Female, n=97	84 (35.4%)	13 (23.2%)		
Age, years, median (Q1, Q3)	64 (52, 73)	72 (69, 78)	8085.50	0.008
Socioeconomic level, *n*, %				
Low, n=8	3 (1.3%)	5 (8.9%)	10015.00	0.008
Medium, n=246	200 (84.4%)	46 (82.1%)	0.17	0.681
Good, n=26	22 (9.3%)	4 (7.1%)	0.26	0.420
Non-mentioned, n=13	12 (5.1%)	1 (1.8%)	/	/
Marital status, *n*, %				
Single, n=6	5 (2.1%)	1 (1.8%)	0.02	0.677
Married, n=247	201 (84.8%)	46 (82.1%)	0.24	0.476
Widowed, n=34	27 (11.4%)	7 (12.5%)	0.05	0.816
Non-mentioned, n=6	4 (1.7%)	2 (3.6%)	/	/
Employment, *n*, %				
Yes, n=215	173 (73%)	42 (75.0%)	0.09	0.760
No, n=78	64 (27%)	14 (25.0%)		
Unhealthy habits, *n*, %				
None, n=167	138 (58.2%)	29 (5.2%)	0.77	0.381
Active smoking, n=35	28 (11.8%)	7 (12.5%)	0.02	0.887
Ex-smoker, n=86	66 (27.8%)	20 (35.7%)	1.35	0.245
Traditional combustion, n=35	29 (12.2%)	6 (10.7%)	0.10	0.752
Alcoholism, n=4	3 (1.3%)	1 (1.8%)	0.09	0.763
Medication history, *n*, %				
Yes, n=118	87 (36.7%)	31 (55.4%)	6.55	0.010
No, n=44	41 (17.3%)	3 (5.4%)		
Non-mentioned, n=131	109 (46.0%)	22 (39.3%)	/	/
Comorbidities, *n*, %				
Yes, n=225	176 (74.3%)	49 (87.5%)	4.45	0.035
No, n=68	61 (25.7%)	7 (12.5%)		
In contact with suspected or confirmed COVID–19 subjects, *n*, %				
Yes, n=121	100 (42.2%)	21 (37.5%)	0.41	0.521
No, n=172	137 (57.8%)	35 (62.5%)		
Time between the onset of symptoms and hospitalization, d, median (Q1, Q3)	7 (7, 10)	8 (6, 10)	5762.50	0.919
Respiratory rate, cycles/minute, median (Q1, Q3)	24 (22, 26)	25 (24, 30)	2432.50	0.027
Partial oxygen saturation (SpO_2), %, median (Q1, Q3)	86 (80, 89)	79 (74, 86)	3558.00	0.001
Mean heart rate, bpm, mean±SD	96.99±14.07	99.44±16.49	2789.50	0.634
Weight, kg, mean±SD	83.45±13.97	73.80±20.29	177.50	0.172

3.3. COVID–19 clinical signs and symptoms

The time between the onset of symptoms and hospitalization was [7 (7, 10)] d in the infection group. In infection group, main symptoms were dyspnoea [268 (91.5%)], asthenia [264 (90.1%)], fever [193 (65.9%)], dry cough [176 (60.1%)], anorexia [170 (58.0%)], chest pain [96 (32.8%)], productive cough [93 (31.7%)], profuse sweating [83 (28.3%)], diarrhoea [69 (23.5%)], nausea [69 (23.5%)], anosmia [64 (21.8%)], ageusia [59 (20.1%)], weight loss [56 (19.1%)], vomiting [46 (15.7%)], throat irritation [31 (10.6%)], burning of the urine [26 (8.9%)], abdominal pain [22 (7.5%)] and dysuria [19 (6.5%)]. The main symptoms in the control group included pneumothorax, haemoptysis, asthma, chronic obstructive pulmonary disease, tuberculosis, and specific treatment intolerance, tumoral process, *etc*.

Polypnoea was more frequent in the infection group compared with the control group (P<0.001) and particularly pronounced in severe cases compared with the non-severe group (P=0.027). Patients with normal lung auscultation were more in the infection group (*OR*: 2.567, 95% *CI*: 1.314-5.013, P<0.05) (Tables 1&2).

On admission, the median respiratory rate, partial oxygen saturation (SpO_2), the mean heart rate, and weight were 25 *vs*. 23 cycles/minute, 85% *vs*. 94%, (97.43±14.51) *vs*. (94.82±15.61) bpm, (81.81±15.45) *vs*. (67.65±15.83) kg in the infection and control groups, respectively. Table 2 demonstrates that SpO_2 was significantly lower in infected patients and in severe cases with higher respiratory rates. Figure 2A shows that SpO_2 on admission was effective in COVID-19 diagnosis with a sensitivity of 91.6%.

3.4. Chest CT and laboratory tests

Chest-CT was performed on 267 (91.1%) COVID-19 patients with 151 (51.5%) typical and 91 (31.1%) compatible radiological pictures. Whilst, 25 (8.5%) showed non-evocative chest-CT of

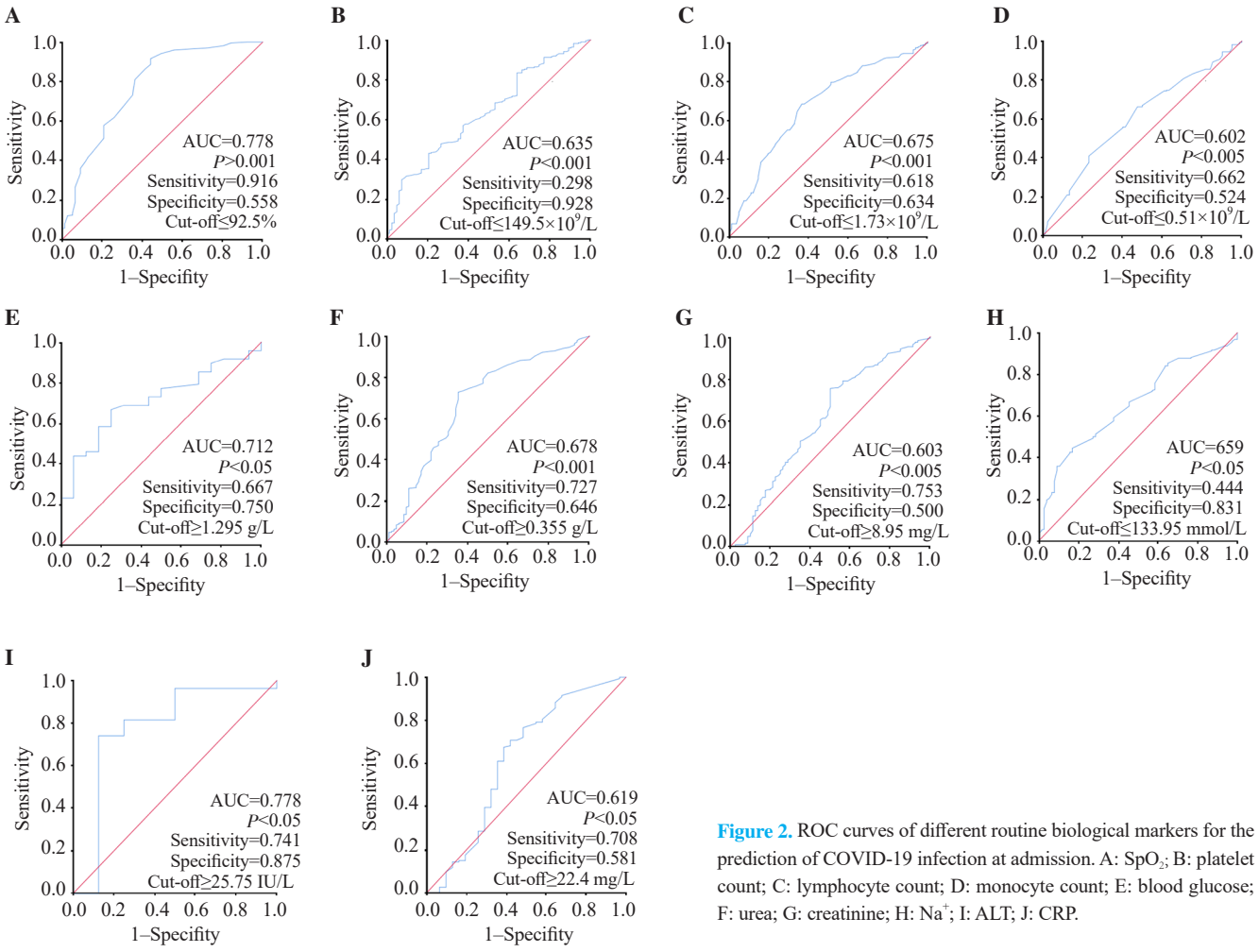

Figure 2. ROC curves of different routine biological markers for the prediction of COVID-19 infection at admission. A: SpO_2; B: platelet count; C: lymphocyte count; D: monocyte count; E: blood glucose; F: urea; G: creatinine; H: Na^+; I: ALT; J: CRP.

Table 3. Chest CT and laboratory test result .

Tests	Non–severe group, *n*=237	Severe group, *n*=56	χ^2	*P*
Chest–CT, *n*=267, *n*, %				
<10%, *n*=17	16 (6.8%)	1 (1.8%)	2.043	0.129
10%-25%, *n*=71	62 (26.2%)	9 (16.1%)	2.511	0.113
26%-50%, *n*=102	87 (36.7%)	15 (26.8%)	1.965	0.161
51%-75%, *n*=58	43 (18.1%)	15 (26.8%)	2.131	0.144
>75%, *n*=14	11 (4.6%)	3 (5.4%)	0.051	0.521
RT–PCR, *n*=72, *n*, %				
Positive, *n*=51	37 (15.6%)	14 (25.0%)	2.820	0.244
Serology test, *n*=58, *n*, %				
Positive, *n*=28	22 (9.2%)	6 (10.8%)	0.263	0.877
Antigenic test, *n*=53, *n*, %				
Positive, *n*=46	38 (16.0%)	8 (14.3%)	1.864	0.394

COVID-19. As for the extent of lung damage, the infection at minim (< 10%), mild (10%-25%), moderate (26%-50%), severe (51%-75%) and critical (>75%) levels were found in 17 (5.8%), 71 (24.2%), 102 (34.8%), 58 (19.8%) and 14 (4.8%) of cases, respectively. The lung damage extent was not mentioned in 5 files. Table 3 doesn't show any differences between severe and non-severe patients. Chest-CT was prescribed for only 24 non-COVID-19 patients and none of them was in favour of COVID-19.

Real-time polymerase chain reaction (RT-PCR) was prescribed in 72 (24.6%) infected patients, of which 51 (17.4%) came back positive. Whereas, serology and antigenic test were in favour of COVID-19 in 28 (9.6%) and 46 (15.7%), respectively. Table 3 dosen't show any differences in these tests between severe and non-severe cases.

3.5. Hemo–biochemical markers

Tables 4&5 show higher neutrophils and white blood cells (WBC), but lower lymphocyte, and platelet counts among infected patients, particularly in the severe subgroup, during admission and/

or follow-up (all $P<0.05$). While higher international normalized ratio (INR) and D-dimer values and lower prothrombin ratio (PR) were observed only in the severe subgroup and lower monocyte count in the COVID-19 group (all $P<0.05$). However, there were no differences in fibrinogen (which was exclusively prescribed for COVID-19 patients during follow-up) [(5.43±1.59) and (5.41±0.87) g/L, $P=0.983$] or hemoglobin (Hb) levels in all cases in the infection, control, non-severe and severe groups were (13.66±1.79), (14.02±1.20), (13.72±1.71), and (13.39±2.13) mg/dL on admission, $P=0.124$ and $P=0.242$, respectively) and (13.07±2.13), (13.48±1.87), (13.50±1.83), and (13.41±2.04) mg/dL during follow-up, $P=0.246$ and $P=0.837$, respectively). Figures 2B-D, and 3A-D show that WBC, neutrophil, lymphocyte, monocyte, and platelet counts were effective in COVID-19 diagnosis at admission and/or during follow-up.

Infected patients had higher blood glucose levels at admission and follow-up than control cases ($P<0.05$), but there was no significant difference between severe and non-severe groups. During follow-up, COVID-19 patients had higher triglyceride (TG) levels than the control group ($P<0.05$) (Tables 4&5). Figures 2E, 3E, and 3H show glucose and TG were effective in diagnosis.

Tables 4&5 demonstrate that urea was higher in COVID-19 patients at admission and/or during follow-up and creatinine was higher in severe patients ($P<0.05$). COVID-19 patients had lower Na^+ on admission while severe cases had higher K^+ during follow-up ($P<0.05$). Figures 2F, 2G and 3F show that renal markers were interesting in COVID-19 diagnosis.

Infected cases had higher transaminases [alanine aminotransferase (ALT), aspartate aminotransferase (AST)], and lower albumin at admission and/or during follow-up ($P<0.05$) (Tables 4&5). However, transaminases and albumin did not impact the severity of the disease. As shown in Figures 2I anf 3G-I, transaminases and albumin were effective in COVID-19 diagnosis at admission and/or during follow-up.

Table 4. Biochemical parameters of control group and infection group ($n=381$).

Parameters	Control group, $n=88$	Infection group, $n=293$	*U/t*	*P*
WBC, $\times10^9$/L, median (Q1, Q3)				
Admission	10.83 (8.60, 14.70)	10.70 (7.63, 13.90)	12515.5	0.134
Follow-up	9.17 (6.85, 11.44)	11.00 (7.99, 13.77)	2350.5	0.024
Lymphocytes, $\times10^9$/L, median (Q1, Q3)				
Admission	2.05 (1.30, 2.70)	1.30 (0.90, 2.00)	14951.5	0.000
Follow-up	1.67 (1.14, 2.10)	0.93 (0.67, 1.40)	3270.0	0.000
Monocytes, $\times10^9$/L, median (Q1, Q3)				
Admission	0.58 (0.40, 0.83)	0.40 (0.30, 0.70)	13285.5	0.005
Follow-up	0.51 (0.39, 0.72)	0.34 (0.20, 0.58)	2914.0	0.002
Neutrophils, $\times10^9$/L, median (Q1, Q3)				
Admission	8.35 (5.98, 12.40)	8.50 (5.75, 11.60)	10410.5	0.922
Follow-up	6.41 (8.96, 4.42)	9.61 (12.80, 6.87)	922.5	0.001
Platelets, $\times10^9$/L, median (Q1, Q3)				
Admission	228.0 (187.0, 307.0)	200.0 (139.0, 262.0)	14330.5	0.000
Follow-up	224.0 (185.0, 281)	222.0 (156.0, 287.0)	2618.5	0.092
PR on admission, %, median (Q1, Q3)	79.0 (70.0, 92.0)	80.4 (70.0, 95.0)	7024.0	0.439
INR on admission, median (Q1, Q3)	1.15 (1.06, 1.26)	1.14 (1.04, 1.24)	–7715.5	0.534
D–dimer during follow–up, ng/mL, median (Q1, Q3)	1410.1 (721.9, 7858.2)	555.5 (401.0, 976.0)	269.5	0.073
Blood glucose, g/L, median (Q1, Q3)				
Admission	1.08 (0.93, 1.34)	1.50 (1.07, 2.11)	221.5	0.012
Follow-up	1.24 (0.95, 1.68)	2.00 (1.38, 3.47)	1116.5	0.000
Urea, g/L, median (Q1, Q3)				
Admission	0.30 (0.23, 0.46)	0.44 (0.33, 0.60)	7331.5	0.000
Follow-up	0.34 (0.25, 0.46)	0.53 (0.39, 0.68)	1876.5	0.000
Creatinine, mg/L, median (Q1, Q3)				
Admission	7.4 (6.7, 9.1)	9.0 (7.2, 10.6)	8741.5	0.005
Follow-up	9.8 (7.4, 11.5)	9.7 (7.9, 13.0)	2856.5	0.322
Na^+ on admission, mmol/L, mean±SD	136.61±3.70	134.31±5.70	–3.38	0.000
K^+ during follow–up, mmol/L, mean±SD	4.14±0.51	4.09±0.67	–0.51	0.560
AST during follow–up, IU/L, median (Q1, Q3)	21.8 (16.6, 32.0)	27.5 (19.3, 38.8)	2279.5	0.024
ALT, IU/L, median (Q1, Q3)				
Admission	13.4 (9.5, 23.57)	44.0 (21.0, 73.0)	48.0	0.017
Follow-up	15.9 (11.4, 27.3)	32.7 (20.0, 53.0)	1793.0	0.000
CRP on admission, mg/L, median (Q1, Q3)	12.0 (3.0, 96.0)	45.0 (18.0, 92.3)	1817.0	0.036
LDH during follow–up, IU/L, median (Q1, Q3)	194.0 (172.4, 362.8)	303.9 (229.0, 411.0)	289.5	0.013
PCT during follow–up, ng/mL, median (Q1, Q3)	/	/	/	/
Albumin during follow–up, g/L, median (Q1, Q3)	39.0 (35.5, 41.5)	35.6 (31.7, 38.7)	–2197.0	0.002
TG during follow–up, g/L, median (Q1, Q3)	1.27 (0.85, 1.73)	1.52 (1.15, 2.23)	302.0	0.032

SpO_2: partial O_2 saturation; WBC: white blood cells; PR: prothrombin ratio, INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PCT: procalcitonin; LDH: lactate dehydrogenase; CRP: C-reactive protein; TG: triglyceride.

Table 5. Biochemical parameters of severe group and non-severe group (n=293).

Parameters	Non–severe group, n=237	Severe group, n=56	U/t	P
WBC, $\times10^9$/L, median (Q1, Q3)				
Admission	10.20 (7.30, 13.20)	12.40 (8.40, 17.20)	6 874.5	0.005
Follow-up	10.71 (7.76, 12.7)	11.98 (9.52, 16.11)	1 654.0	0.015
Lymphocytes, $\times10^9$/L, median (Q1, Q3)				
Admission	1.40 (0.90, 2.00)	1.10 (0.78, 1.88)	4 611.5	0.262
Follow-up	1.00 (0.72, 1.57)	0.63 (0.45, 1.056)	481.0	0.003
Monocytes, $\times10^9$/L, median (Q1, Q3)				
Admission	0.40 (0.30, 0.68)	0.40 (0.20, 0.70)	4 971.5	0.610
Follow-up	0.37 (0.22, 0.52)	0.29 (0.20, 0.64)	769.5	0.698
Neutrophils, $\times10^9$/L, median (Q1, Q3)				
Admission	8.00 (5.68, 10.93)	10.40 (7.30, 14.90)	6 571.0	0.002
Follow-up	9.34 (6.33, 11.33)	11.60 (8.22, 15.15)	896.0	0.015
Platelets, $\times10^9$/L, median (Q1, Q3)				
Admission	200.0 (133.0, 267.0)	196.0 (145.0, 245.5)	5 354.0	0.826
Follow-up	225.0 (160.5, 296.0)	194.0 (139.0, 250.0)	502.0	0.020
PR on admission, %, median (Q1, Q3)	82.6 (71.0, 98.0)	74.0 (66.0, 82.5)	2 804.5	0.003
INR on admission, median (Q1, Q3)	1.13 (1.01, 1.23)	1.20 (1.12, 1.27)	4 930.0	0.009
D–dimer during follow–up, ng/mL, median (Q1, Q3)	496.0 (370.0, 810.0)	962.7 (646.8, 1 781.4)	1 089.0	0.001
Blood glucose, g/L, median (Q1, Q3)				
Admission	1.50 (1.08, 2.10)	1.83 (0.83, 3.98)	110.0	0.948
Follow-up	2.01 (1.34, 3.30)	1.87 (1.39, 3.59)	598.5	0.760
Urea, g/L, median (Q1, Q3)				
Admission	0.41 (0.31, 0.56)	0.52 (0.41, 0.74)	7 760.5	0.000
Follow-up	0.53 (0.39, 0.66)	0.62 (0.47, 0.88)	1 724.0	0.015
Creatinine, mg/L, median (Q1, Q3)				
Admission	10.0 (8.7, 12.9)	12.3 (10.0, 17.0)	7 527.5	0.000
Follow-up	9.3 (7.6, 12.3)	12.4 (8.9, 20.2)	1 730.5	0.004
Na^+ on admission, mmol/L, mean±SD	134.57±5.95	133.23±4.40	1.466	0.144
K^+ during follow–up, mmol/L, mean±SD	4.01±0.66	4.42±0.65	–2.919	0.004
AST during follow–up, IU/L, median (Q1, Q3)	26.0 (18.0, 39.4)	27.9 (20.7, 42.2)	962.5	0.589
ALT, IU/L, median (Q1, Q3)				
Admission	39.5 (15.0, 73.0)	44.0 (30.5, 50.5)	75.0	0.808
Follow-up	33.0 (20.2, 53.8)	31.2 (19.0, 44.8)	831.5	0.608
CRP on admission, mg/L, median (Q1, Q3)	46.4 (18.0, 92.9)	40.4 (13.5, 86.8)	1 852.0	0.656
LDH during follow–up, IU/L, median (Q1, Q3)	292.4 (223.8, 391.8)	430.9 (292.0, 496.2)	904.0	0.004
PCT during follow–up, ng/mL, median (Q1, Q3)	0.05 (0.05, 0.14)	0.15 (0.11, 0.51)	80.5	0.037
Albumin during follow–up, g/L, median (Q1, Q3)	36.0 (31.7, 38.8)	34.2 (30.5, 37.1)	285.0	0.331
TG during follow–up, g/L, median (Q1, Q3)	1.70 (1.09, 2.26)	1.36 (1.16, 1.89)	140.0	0.665

In the infection group, C-reactive protein (CRP) was higher at admission (P<0.05), but no difference was found between severe and non-severe cases, both at admission and during follow-up (P=0.656 and 0.177, respectively). In contrast, lactate dehydrogenase (LDH) levels increased during follow-up. Furthermore, severely infected patients had higher LDH and procalcitonin (PCT) levels (P<0.05). According to Figures 2J and 3J, only CRP and LDH were effective in diagnosis of COVID-19.

4. Discussion

The risk of severe COVID-19 is higher in males and increases with age[6,9,10]. Older patients with associated comorbidities have a poor prognosis and a high risk[13]. Overall, the signs of COVID-19 included but not limited to fever[3,6,11,12], cough[3,6,11,12], fatigue[3,11,12], muscle soreness[11], chest tightness[11,12], anosmia[3], ageusia[3], myalgia[3,12], shortness of breath[3,12], expectoration[3,12] and digestive signs including diarrhea[3] and nausea/vomiting[3]. Most of these symptoms were also noticed in our study. The variety of symptoms could be explained by the fact that SARS-CoV-2 targets angiotensin-converting enzyme-2 receptors which are expressed in different tissues[1,6].

The confirmation of the diagnosis of COVID-19 relies on specific symptoms and characteristic radiological and biological signs[3]. Most infected patients show chest-CT lesions[1]. Chest-CT was used to confirm the diagnosis in almost all our patients. According to our Unit of Pneumology, the pulmonary damage extend was classified into <10%, 10%-25%, 25%-50%, 50%-75% and ≥75%[3,13].

Despite its limited sensitivity (63%), RT-PCR with nasal swab has been used to confirm COVID-19 in some studies[3,6,14]. And serological tests are usually used to assess SARS-CoV-2 infection. In our study, RT-PCR and serological tests have been poorly examined. During the progression of COVID-19, some biological parameters

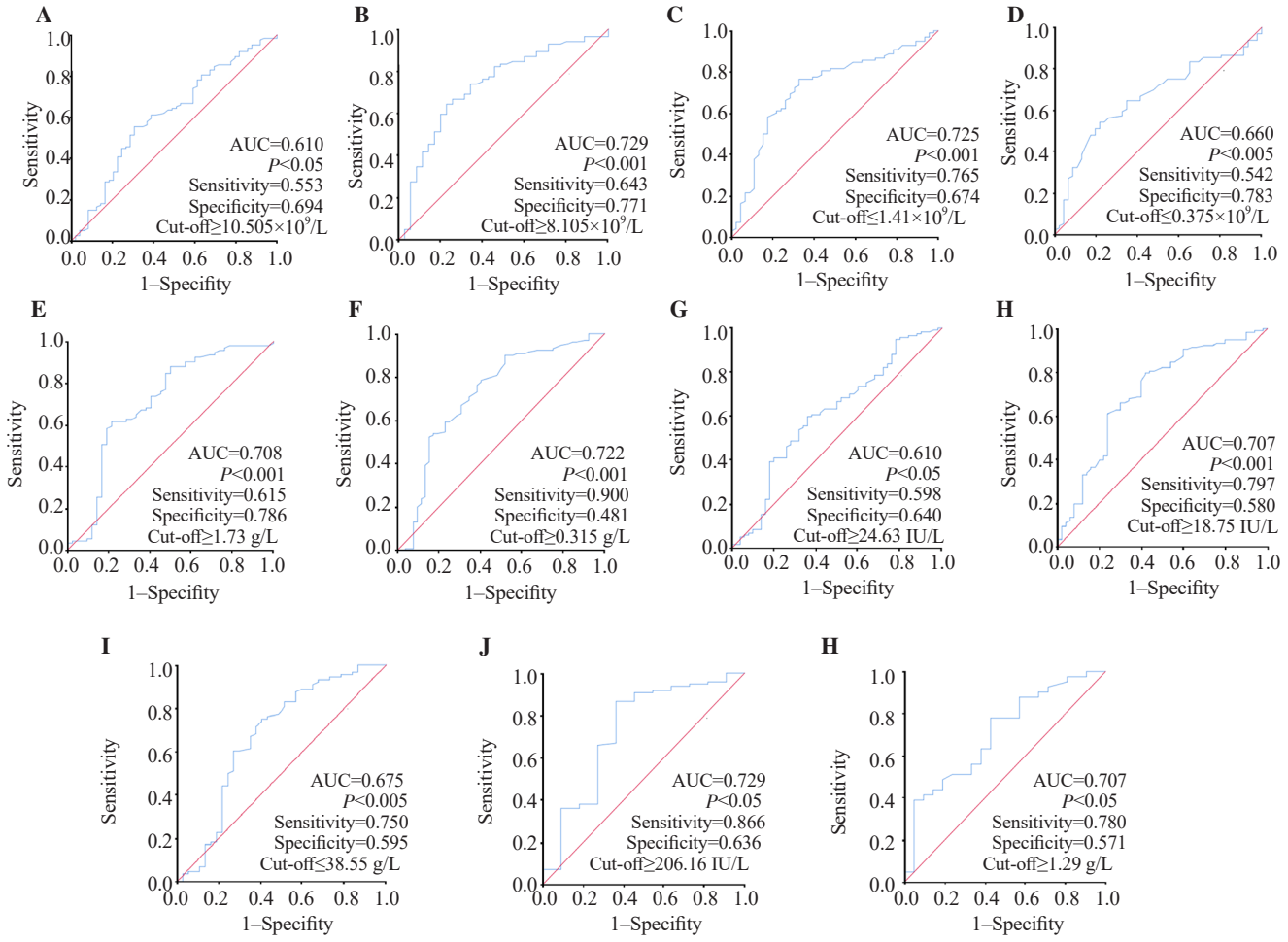

Figure 3. ROC curves of different routine biological markers for the prediction of COVID-19 infection during follow-up. A: WBC; B: neutrophils; C: lymphocyte count; D: monocyte count; E: blood glucose; F: urea; G: AST; H: ALT; I: albumin; J: LDH; H: triglyceride.

are changed abnormally[3,14,15]. As previously reported, anemia and thrombocytopenia appear rare in COVID-19 patients[3]. In contrast, Lippi *et al*.[14] reported a low concentration of Hb. Whereas, neutrophilia, lymphopenia, and leukocytosis have been frequently observed in COVID-19[3,13,14]. In addition, leukocytosis[7,12,16], neutrophilia[16], lymphopenia[7,12,16] and lower monocyte[7,12], eosinophil[7,12], basophil[12], and platelet[7,14] count with lower Hb values[7] have been reported in severe cases.

Results showed that D-dimer levels increase among COVID-19 patients, particularly in those with unfavorable progression which makes it a relevant predictive factor for in-hospital mortality[1,3,5,14,15,17,18]. In our study, the mean of D-dimer concentrations didn't differ between severe and non-severe groups at admission, but it was higher in the severe group during hospitalization. Lippi *et al*.[14] and Kukla *et al*.[19] observed an increase in prothrombin time (PT) while Plaçais *et al*.[3] noticed a decrease in PT, which is similar to our results. In contrast, Kodavoor *et al*.[20] found that PT and INR were normal in most patients. High concentrations of fibrinogen were remarked by Eljilany *et al*.[1] but Grobler *et al*.[15] demonstrated its depletion in COVID-19 patients.

Hyperglycemia has been reported in COVID-19 patients[3,14]. Our results also showed an increased glycemia, particularly in severe subjects. Moreover, elevated serum urea and/or creatinine have been observed in infected patients and they may be associated with a pejorative prognosis[3,7,14,21]. Ok *et al*.[16] remarked that severe cases had higher urea while Poggiali *et al*.[22] found that creatinine increased. Similarly, urea and creatinine levels were higher in COVID-19 patients, especially in the severe group of our study.

Many studies have evaluated the incidence of hepatic abnormalities in SARS-CoV-2 infected patients and showed that transaminase elevations are very common[3,4,6,7,14,19,20,22-24]. In addition, elevation of total bilirubin[20] and hypoalbuminemia[3,7,14,19,22] with normal alkaline phosphatase and γ-glutamyl transpeptidase levels[6,20] have been reported. These abnormalities increased during hospitalization, which is associated with the severity of the infection. In contrast, Wagner *et al*.[23] reported no established link

between high total bilirubin, hypoalbuminemia, and the need for intensive care. The sensitivities and specificities of abnormal AST and ALT to predict mortality were 90.6%, 84.4%, 67.0%, and 89.3% respectively[20]. In our study, higher transaminase levels and lower albuminemia with normal total bilirubin, alkaline phosphatase, and γ-glutamyl transpeptidase were observed in the COVID-19 group. ROC curves showed that AST and ALT could be helpful for the diagnosis of COVID-19 with lower sensitivity and specificity than those recorded in the previous study.

According to previously reported studies, SARS-CoV-2 viral infection induces host defense mechanisms resulting in an inflammation characterized by high levels of inflammatory markers including CRP, PCT, LDH, and ferritin which might be very useful in predicting mild and severe cases[1,7,11,13,14,16,17,22,25,26]. Procalcitonin doesn't increase during viral infection, whilst its gradual increase probably reflects bacterial co-infection in COVID-19 patients[14]. Our findings suggested that CRP levels were higher in the COVID-19 group and PCT was more associated with the outcome. Studies proved that PCT, CRP, and LDH are effective in the diagnosis of COVID-19[11,17,22,26]. In our study, CRP and LDH thresholds were lower than those observed in the previously mentioned studies with different effectiveness.

In conclusion, our results indicated that WBC, neutrophils, lymphocytes, monocytes, platelets, PR, INR and D-dimers, blood glucose, triglycerides, urea, creatinine, Na^+, transaminases, albumin, CRP, PCT, and LDH are useful parameters for diagnosis of COVID-19.

Conflict of interest statement

The authors report no conflict of interest.

Funding

This study received no extramural funding.

Authors' contributions

I.A.: concept, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review; T.B.: literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review; H.B.: literature search, clinical studies, data acquisition, data analysis, manuscript preparation; W.T.: literature search, clinical studies, data acquisition, manuscript preparation; F.D. and F.K.: guarantor.

References

[1] Eljilany I, Elzouki AN. D-Dimer, fibrinogen, and IL-6 in COVID-19 patients with suspected venous thromboembolism: A narrative review. *Vasc Health Risk Manag* 2020; **16**: 455-462.

[2] Bartziokas K, Kostikas K. Lactate dehydrogenase, COVID-19 and mortality. *Med Clin (Barc)* 2021; **156**: 37.

[3]Plaçais L, Richier Q. COVID-19: Caractéristiques cliniques, biologiques et radiologiques chez l'adulte, la femme enceinte et l'enfant. Une mise au point au cœur de la pandémie. *La Rev Méd Int* 2020; **41**: 308-318.

[4] Bangash MN, Patel J, Parekh D. COVID-19 and the liver: Little cause for concern. *Lancet Gastroenterol Hepatol* 2020; **5**: 529-530.

[5] Chocron R, Duceau B, Gendron N, Ezzouhairi N, Khider L, Trimaille A, et al. D-dimer at hospital admission for COVID-19 are associated with in-hospital mortality, independent of venous thromboembolism: Insights from a French multicenter cohort study. *Arch Cardiovasc Dis* 2021; **114**: 381-393.

[6] Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; **73**: 566-574.

[7] Henry BM, De-Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. *Clin Chem Lab Med* 2020; **58**: 1021-1028.

[8] Serrano-Lorenzo P, Coya ON, López-Jimenez A, Blázquez A, Delmiro A, Lucia A, et al. Plasma LDH: A specific biomarker for lung affectation in COVID-19? *Pract Lab Med* 2021; **25**: e00226.

[9] McLaughlin KM, Bechtel M, Bojkova D, Münch C, Ciesek S, Wass MN. et al. COVID-19-related coagulopathy—Is transferrin a missing link? *Diagnostics* 2020; **10**: 539.

[10]Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. *Proc R Soc B Biol Sci* 2015; **282**: 20143085.

[11]Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol* 2020; **127**: 104370.

[12]Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020; **71**: 762-768.

[13]Bouchla A, Kriebardis AG, Georgatzakou HT, Fortis SP, Thomopoulos TP, Lekkakou L, et al. Red blood cell abnormalities as the mirror of SARS-CoV-2 disease severity: A pilot study. *Front Physiol* 2022; **12**: 1-9.

[14]Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med* 2020; **58**: 1131-1134.

[15]Grobler C, Maphumulo SC, Grobbelaar LM, Bredenkamp JC, Laubscher GJ, Lourens PJ, et al. COVID-19: The rollercoaster of fibrinogen, D-dimer, von Willebrand factor, P-selectin and their interactions with endothelial cells, platelets and erythrocytes. *Int J Mol Sci* 2020; **21**: 5168.

[16]Ok F, Erdogan O, Durmus E, Carkci S, Canik A. Predictive values of blood urea nitrogen/creatinine ratio and other routine blood parameters on disease severity and survival of COVID-19 patients. *J Med Virol* 2021; **93**: 786-793.

[17]Huang Y, Lyu X, Li D, Wang L, Wang Y, Zou W, et al. A cohort study of 676 patients indicates D-dimer is a critical risk factor for the mortality of COVID-19. *PLoS One* 2020; **15**: e0242045.

[18]Oualim S, Abdeladim S, Elouarradi A, Bensahi I, Hafid S, Naitelho A, et al. Elevated levels of D-dimer in patients with COVID-19: Prognosis value. *Pan Afr Med J* 2020; **35**: 105.

[19]Kukla M, Skonieczna-Żydecka K, Kotfis K, Maciejewska D, Łoniewski I, Lara LF, et al. COVID-19, MERS and SARS with concomitant liver injury—Systematic review of the existing literature. *J Clin Med* 2020; **9**: 1420.

[20]Kodavoor Vadiraj P, Thareja S, Raman N, Karantha SC, Jayaraman M, Vardhan V. Does raised transaminases predict severity and mortality in patients with COVID 19? *J Clin Exp Hepatol* 2022; **2507**: 1-9.

[21]Nogueira SÁR, Oliveira SCSD, Carvalho AFMD, Neves JMC, Silva LSVD, Silva Junior GBD, et al. Renal changes and acute kidney injury in COVID-19: A systematic review. *Rev Assoc Med Bras* 2020; **66**: 112-117.

[22]Poggiali E, Zaino D, Immovilli P, Rovero L, Losi G, Dacrema A, et al. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in COVID-19 patients. *Clin Chim Acta* 2020; **509**: 135-138.

[23]Wagner J, Garcia-Rodriguez V, Yu A, Dutra B, Larson S, Cash B, et al. Elevated transaminases and hypoalbuminemia in COVID-19 are prognostic factors for disease severity. *Sci Rep* 2021; **11**: 10308.

[24]Pott-Junior H, Bittencourt NQP, Chacha SFG, Luporini RL, Cominetti MR, Anibal FDF. Elevations in liver transaminases in COVID-19: (How) Are they related? *Front Med* 2021; **8**: 1-6.

[25]Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, Bajracharya T, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. *PLoS One* 2021; **16**: e0256744.

[26]Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. *Am J Emerg Med* 2020; **38**: 1722-1726.