Hematological and biochemical parameters can triage COVID-19 patients

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Abstract
Objectives: To reveal the importance of the laboratory routine determination of some hematological, coagulation and biochemical parameters in the prognosis of COVID-19.
Materials and methods: The basic characteristic information such as age, gender, clinical symptoms and the clinical laboratory data of 300 COVID-19 patients that were admitted to the Respiratory Care Unit, Al-Imam Al-Hussein Medical City, Kerbala, Iraq were obtained from the patients' records. The patients were146 males and 154 females, their ages were between 20 and 50 years (34.3±8.6).
Results: According to their clinical status, patients were divided into moderate and severe groups. Among the 300 patients, 177 were considered as moderate cases and 123 were severe cases. Ferritin, D-Dimer, and C-reactive protein (CRP) levels were significantly higher in severe cases (P<0.05), as were lymphocytes and white blood cells (WBC) levels (P=0.0001). Hematocrit and hemoglobin were at almost the same levels in both groups (P>0.05). Platelet counts showed normal values in moderate and severe cases. In severe cases, lactate dehydrogenase (LDH) was significantly increased (P=0.0001). The receiver operating characteristic (ROC) curve exhibited that WBC, D-Dimer and LDH have fair values regarding the discriminative ability between the moderate and severe groups (AUC 0.788, 0.718 and 0.761, respectively, P-value of 0.0001).
Conclusion: The laboratory routine determination is of a key importance in the prognosis and handling of the cases of COVID-19, especially those that could develop acute respiratory failure, so further deterioration can be avoided.
Keywords: SARS-COV-2, Ferritin, C-reactive protein, D-dimer, lactate dehydrogenase.

1.Introduction

Since the coronavirus disease 2019 (COVID-19) outbreak in China, national efforts to contain its spread have been made[1]. Despite all the efforts, the disease has spread to most countries in the world. Until the time of writing and according to reports of the World Health Organization, Iraq was the second country in the Middle East region with the number of the casualties.
COVI-19 caused by the novel coronavirus (n2019-COV), the virus was isolated by Zhu and co-workers early in the pandemic. It was later called severe acute respiratory syndrome coronavirus-2 (SARS-COV-2)[2]. It is an RNA virus and a member of the Coronaviridae family, it infects both humans and animals[3].
It was reported that 80% of people that infected with COVD-19 have mild to moderate symptoms, severe cases constitute 13.8% and 6.1% of the cases have critical illness [4]. Severe cases could deteriorate to immune system dysfunction, rapid damage to multiple organs or even death[5]. As a result, identifying severe cases is critical for precise management, which includes organ support, antiviral medication usage and the preparation of the units of the intensive care.
It was found that changes that occur in the COVID-19 patients' blood can be potential in determining the disease severity and giving the guidance in the diagnosis and treatment of most cases[2], [6]. It was thought that some immune parameters, coagulation parameters, inflammation parameters and hematological parameters could be possible prognostic markers of COVID-19[7]–[10]. On the other hand, it is unclear whether the changes in all of these parameters are caused by the disease itself or predispose to virus infection. Therefore, a lot of investigations are needed to establish the potential role of hematological, coagulation and biochemical parameters in the investigation and diagnosis of this disease.
This study investigates the importance of the routine determination of some hematological and biochemical markers in COVID-19 diagnosis and progression.

2.Materials and methods

2.1.Patients

A total of 300 COVID-19 patients were recruited from the Respiratory Care Unit, Al-Imam Al-Hussein Medical City, Kerbala, Iraq. The SARS-COV-2 infection was detected in the patients according to the reverse transcriptase-polymerase chain reaction

doi.org/10.31838/hiv23.02.214 Received: 07.10.22, Revised: 16.11.22, Accepted: 23.12.22

(RT-PCR) test. The participants (146 males and 154 females) were aged between 20 and 50 years with a mean age of 34.3±8.6. Among these 300 cases, 177 were diagnosed as moderate and 123 were diagnosed as severe. Each one of the patients had a dry cough and a fever, which are COVID-19's most common symptoms, these symptoms ranged from mild to severe in different patients. Patients that had bacterial infection and viral hepatitis, and patients with a history of hematologic disease, autoimmune disease, or tumors were excluded.

2.2.Data collection

The basic characteristic information such as age, gender, the clinical symptoms and the clinical laboratory data of the patients were obtained from their records.

2.3.Statistical analysis

Statistical Package for the Social Sciences (SPSS.23) software was used to perform the statistical analysis. Student's T-test was performed to calculate the mean of the numerical parameters. Receiver operating characteristic (ROC) curve and area under the curve (AUC) was performed to determine the valuable parameters that can triage the moderate and severe cases. P-value < 0.05 was regarded to be statistically significant.

3.Results

According to their clinical assessment, the three hundred COVID-19 patients were divided into two groups; moderate (177 cases, 59%) and severe (123 cases, 41%). The age showed no significant difference between the two groups (Table1). The patients were male (146 patients, 48.6%) and female (154 patients, 51.3%).

Ferritin, C-reactive protein (CRP) and D-Dimer were markedly increased in severe cases (P<0.05). Lymphocytes and white blood cells (WBC) were also markedly elevated in severe cases (P=0.0001), hematocrit and hemoglobin were in almost the same levels in both groups (P>0.05). Platelets counts showed normal values in moderate and severe cases. Lactate dehydrogenase (LDH) was markedly higher in severe cases (P=0.0001) (Table 1).

The ROC curve was performed to detect the laboratory markers that have the discriminative power to triage moderate and severe groups (Figure 1). The ROC curve showed that only WBC, D-Dimer and LDH have fair values regarding the discriminative ability between the two groups (AUC 0.788, 0.718 and 0.761 respectively with P-value of 0.0001), while CRP, ferritin, platelets, LDH and RBS showed poor discriminative ability (AUC <0.7) (Table 2).

Table 1: The distribution of age, some hematological, coagulation and some biochemical parameters of patients with COVID-19.

Parameters	Total (n=300) Mean ±SE	Moderate (n=177) Mean ±SE	Sever (n=123) Mean ±SE	P-value
Age (year)	34.52±0.48	34.34±0.65	34.78±0.73	0.655
CRP (mg/L)	65.28±4.22	54.65±4.95	80.41±7.25	0.002
Ferritin (ng/mL)	672.70±24.82	564.32±35.35	736.54±31.34	0.001
D-Dimer (ng/mL)	671.39±91.46	499.45±95.67	918.80±173.65	0.024
WBC $\times 10^9$/L	10.097±0.26	8.558±0.28	12.538±0.41	0.0001
Lymphocyte $\times 10^9$/L	1.704±0.057	1.953±0.083	1.34±.055	0.0001
Platelets $\times 10^9$/L	260.45±5.27	247.62±6.95	278.91±7.81	0.003
Hematocrit %	41.93±1.73	43.93±2.91	39.06±0.53	0.168
HB	12.69±0.10	12.80±0.13	12.53±0.18	0.230
LDH (U/L)	417.27±10.96	335.16±6.20	535.43±21.07	0.0001

SE: Standard error of the mean, HB: Hemoglobin.

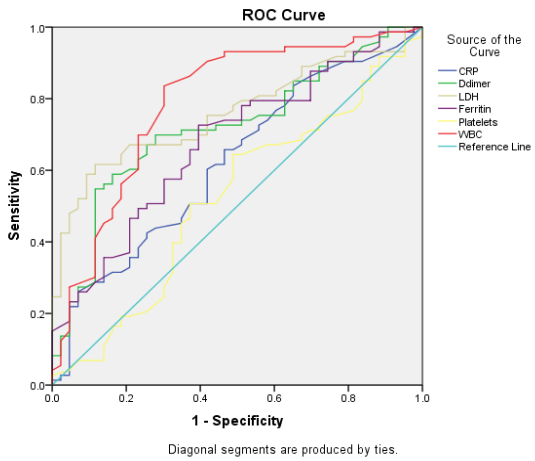

Figure 1: ROC curve using combined parameters (CRP, D-Dimer, LDH, ferritin, platelets and WBC) to identify the severe COVID-19 cases from moderate cases.

Table 2: ROC analysis of some study parameters.

Parameters	AUC	SE	P-value	95% CI	
				LB	UB
CRP	0.621	0.053	0.029	0.517	0.726
Ferritin	0.676	0.051	0.002	0.577	0.776
D-Dimer	0.718	0.049	0.0001	0.623	0.813
WBC	0.788	0.046	0.0001	0.697	0.878
Platelets	0.520	0.056	0.714	0.410	0.631
LDH	0.761	0.044	0.0001	0.675	0.846

AUC: Area under curve.

4.Discussion

The SARS-COV-2 belongs to the Coronaviridae family of viruses. It is distinct from other viruses in this family that cause common cold in humans, and it is like SARS-CoV, which caused SARS in 2003, and

Middle East respiratory syndrome coronavirus (MERS-COV), which caused MERS in 2012[11].

Urgent identification of the laboratory parameters that could help in predicting the progression of COVID-19 is definitely needed. These predictors will enable proper intensive care unit preparations and risk stratification. Moreover, identification of the laboratory parameters that are able to discriminate between severe and moderate cases will allow improve clinical awareness.

The analysis of hematological parameters is one of the most widely required analysis in the clinics, and it is the most performed test in the laboratories. In COVID-19 pandemic, complete blood count (CBC) test could reflect the changes in the peripheral blood and immune system that are caused by the disease[12].

The findings of this study showed significant increasing in WBC and lymphocyte (P= 0.0001) in the patients who were severe cases compared with moderate cases. These findings are consistent with Wang *et al.*[9]. These results confirm the vigorous response of the immune system against SARS-COV-2. Meanwhile, hematocrit and HB showed no significant difference between the severe and moderate groups (P>0.05). Platelet counts showed normal values in moderate and severe cases with 11 patients (0.036 %) showed mild thrombocytopenia (platelet count 96-150 × 10^9/L). These results agree with Fan *et al* in their study on chines and Malayan population[13].

With respect to inflammation biomarkers, CRP and ferritin, the acute-phase proteins, were dramatically increased in all COVID-19 patients compared to their normal ranges, however they showed significant increase in the patients with severe illness compared to patients with moderate illness (P= 0.002) and (P=0.001), respectively. These findings were compatible with Onur *et al* and Li *et al.* [5], [14]. C-reactive protein is synthesized in the liver in response to interleukin-6 and has been reported in many viral infections including COVID-19[15].

In this study, despite that CRP was significantly different between the moderate and severe cases, it failed to give a good discriminative indication (AUC of ROC analysis was 0.621), this could be due to its fast elevation within the early stage of the disease course. Although other study by Wang reported that CRP level reflects the lung lesions and it is a good indicator of disease severity[9].Nevertheless, it is believed that the combination of elevated CRP and lymphopenia could effectively differentiate COVID-19 patients from patients with other viral infections[15].

The main function of ferritin is to store iron. After conversion from Fe (II) to Fe (III), iron is stored in ferritin. The oxidation of Fe (II) to form Fe (III) is important to protect the cell, because Fe (II) can oxidize hydrogen peroxide to form a highly toxic hydroxyl free radical. Ferritin is up-regulated in infectious and non-infectious inflammation[16]. In their research on 301 Turkish patients that were hospitalized because of COVID-19, Onur *et al* reported that ferritin was significantly high in the patients, especially the non-survivor ones [14].In their retrospective study on 147 Chinese COVID-19 patients, Lin *et al.* reported that serum ferritin was markedly increased in the patients with severe cases compared with the moderate ones (P=0.0001), they consider serum ferritin as an important risk factor of the disease severity (AUC=0.748, P<0.0001)[17].

This study found that, even though serum ferritin levels were significantly higher in severe cases, ROC analysis revealed that this test could not fairly differentiate between moderate and severe cases (AUC = 0.76, P = 0.002, 95% CI = 0.577-0.776). This could be due to the already elevated levels of serum ferritin in patients with moderate cases, yet this study confirmed what other literature illustrated about considering serum ferritin as a good biomarker in the prognosis of COVID-19[14], [17]–[19].

D-dimer is routinely assayed to detect the formation of thrombosis, it is produced when plasmin cleaves thrombin to destroy the blood clot. There are many processes that increase the plasmin formation thus increasing the plasma D-dimer. Examples include intravascular coagulation, arterial thrombosis, cancer, pregnancy and inflammation[20]. Yao and *et al.*, in their retrospective study, concluded that D-dimer is a good prognostic marker; elevated levels of D-dimer are associated with mortality in hospitalized patients with COVID-19[21]. Our results showed that D-dimer is increased in all COVID-19 cases, but it is significantly increased in severe cases compared with moderate cases (P=0.024) (Table 1). According to ROC analysis, D-dimer showed fair discriminative power to triage the severe cases from the moderate ones (AUC=0.718, P=0.0001) (Table 2, Figure 1).

Lactate dehydrogenase (LDH) is an enzyme responsible for converting pyruvate to lactate in the cells. LDH levels in the plasma rise as a result of tissue injury, and it is regarded as a non-specific marker of cellular death caused by a variety of diseases[22]. Many researchers tried to follow the change of plasma LDH in COVID-19 patients, Akdogan and his co-workers found that plasma LDH was significantly elevated in COVID-19 patients and that LDH is a possible predictor of COVID-19 severity[23]. Our findings are compatible with the findings of Akdogan *et al* on Turkish patients and with Wu *et al* on Chinese patients; our results showed a marked increase in plasma LDH in the severe group of patients compared to the moderate group. As well as a fair discriminative power was obtained from LDH levels by ROC analysis (AUC=0.761, P=0.0001) (Table 2, Figure 1).

5.Conclusion

The routine determination of some hematological and biochemical parameters can aid in the prognosis and flow of COVID-19. Our research showed that WBC, lymphocyte, CRP, D-dimer, ferritin and LDH are increased in COVI-19 patients, in the same time,

these parameters are markedly elevated in patients who had severe illness compared to the moderate cases. These facts make the laboratory routine determination of these parameters of key importance in the prognosis and handling the cases of COVID-19, especially those that could develop acute respiratory failure, so further deterioration can be avoided.

Ethical approval: The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 2021HU2 (including the number and the date in 1/9/2021) to get this approval.

List of abbreviations

COVID-19: Coronavirus disease 2019, SARS-COV-2: Severe acute respiratory syndrome coronavirus-2, MERS-COV: Middle East respiratory syndrome coronavirus, ROC: Receiver operating characteristic, CRP: C-reactive protein, LDH: Lactate dehydrogenase.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding: Self-funding

Limitation of the study: The sample size of the study is somewhat small, larger sample size could be more accurate in reflecting the impact of the routine work on the diagnosis and prognosis of COVID-19.

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