

Early Identification of COVID-19 Patients Using Hematological Profile and Biochemical Parameters

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Abstract

COVID-19 patients showed changes in biochemical and hematological parameters which may cause other complications. D-dimer is one of the prognostic biomarkers used to predict COVID-19 infection, the elevated level of it considered one of the risk factors for mortality especially in adult COVID-19 patients and indicated the positive correlation between D-dimer and disease severity. Another biochemical biomarker is ferritin and CRP, which consider a key mediators of the immune dysregulation via direct immune suppressive and contributing to cytokine storm. This suggested the ferritin and CRP level might be considered a crucial factor influencing the severity of COVID-19. SARS-COV-2 also has affected the regulation of the immune response through an impaired immune system which includes lymphopenia, monocyte, and granulocyte abnormalities, as well as causes inflammatory immune response through elevated levels of cytokines, especially in COVID-19 critical cases. The aim of this study is the identification of COVID-19 patients by using hematological and biochemical Parameters. This study included 180 individuals of a variety of ages and both sexes, the subjects included 60 individuals who participated as healthy control RT-PCR COVID-19 negative, and 120 participants were introduced as COVID-19 patients were diagnosed by RT-PCR test from nasopharyngeal swabs. Based on the disease severity the patients were grouped into two groups each of which consisted of 60 patients, which included the mild-moderate group and the severe group. All participated were subjected to laboratory tests which included hematological and biochemical tests. Result of this study reveal that median of CRP, Ferritin, and D-dimer level in severe group higher than in other group's mild-moderate and control. While median of monocyte count in mild-moderate group higher than in both control and severe group. Median of Lymphocyte count in control group higher than in both patients groups severe and mild-moderate. On other side the neutrophil median in severe group was higher than in another group's mild-moderate and control.

The result among NLR was reveal the median in severe group higher than mild-moderate and control with highly significant different. The data present in this current study reveal the alterations

among biochemical and hematological parameters in COVID-19 patients correlated significantly with disease severity and propagation and can used as prognostic predictive markers for disease severity.

Keywords: COVID-19, Lymphopenia, D-dimer, ferritin CRP, SARS-COV-2.

التحديد المبكر لمرضى كوفيد-19 باستخدام الملف الدموي ومعايير الكيمياء الحيوية

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الخلاصة

أظهر مرضى كوفيد-19 تغيرات في المعايير البيوكيميائية والدموية والتي قد تسبب مضاعفات أخرى. يعد الدايمر احد المؤشرات الحيوية والمستخدم للتعقب بعدوى كوفيد-19, ويعتبر المستوى المرتفع له احد عوامل الخطر لزيادة معدل الوفيات خاصة عند مرضى كوفيد-19 البالغين مما يؤكد العلاقة الايجابية بين الدايمر وشدة المرض. من العلامات الحيوية الاخرى هي الفيريتين والبروتين المتفاعل نوع (س), والتي تعتبر وسيط رئيسي لخلل التنظيم المناعي عن طريق التنشيط المناعي المباشر والمساهمة في عاصفة السيتوكين, وهذا يشير الى انه يمكن اعتبار مستوى هذه المؤشرات عاملاً اساس يؤثر على شدة كوفيد-19. لقد أثر سارس-كوفيد-2 على تنظيم الاستجابة المناعية من خلال اضعاف الجهاز المناعي الذي يؤدي الى قلة الخلايا للمفاوية, وعدم انتظام الخلايا الوحيدة والخلايا المحببة, كما يسبب استجابات مناعية التهابية من خلال ارتفاع مستويات السيتوكينات خاصة في الحالات المرضية الحرجة. الهدف الاساسي من هذه الدراسة هو استخدام المعايير البيوكيميائية الحيوية والدموية لتحديد اصابة مرضى كوفيد-19. شملت هذه الدراسة 180 فرداً من مختلف الأعمار ومن كلا الجنسين, تم التقسيم الى مجموعتين, مجموعة السيطرة وتشمل 60 شخصاً سليمين غير مصابين بالمرض حيث كانوا سالبين لنتيجة تفاعل البلمره الخاص بالكشف عن المرض, و120 شخص اخرين كانوا مصابين بالمرض وتم تأكيد الاصابة عن طريق تفاعل البلمرة من مسحات البلعوم الأنفي. تم تقسيم المصابين (120 شخص) الى مجموعتين بناءً على شدة المرض, كل مجموعة تشتمل على 60 مريضاً, والتي شملت المجموعة الخفيفة-المتوسطة والمجموعة الشديدة. تم اخضاع جميع المشتركين الى الفحوصات المخبرية التي شملت اختبارات الدم واختبارات الكيمياء الحيوية. كشفت نتائج هذه الدراسة ان متوسط البروتين التفاعلي نوع (س) والفيريتين والدايمر اعلى بشكل ملحوظ في مجموعة المرضى شديدة المرض مقارنة بالمجموعة الضابطة و مجموعة المرضخفيفة – متوسطة المرض مع وجود فروق ذات دلالة احصائية. كان متوسط عدد الخلايا أحادية الخلية في مجموعة المرضى الخفيفة-المتوسطة أعلى منه في كلا المجموعتين الشديدة والضابطة مع وجود فروق غير معنوية. كان الوسيط اقل بشكل ملحوظ لتعدد الخلايا للمفاوية في المرضى الذين يعانون من كوفيد-19 مقارنة مع المجموعة الضابطة مع وجود فروق ذات دلالة احصائية. ايضا فرق معنوي كبير بين نسبة العدلات والخلايا للمفاوية للمرضى الذين يعانون من اصابة شديدة مقارنة مع مجموعة المرضى الخفيفة-المتوسطة والمجموعة الضابطة. تكشف البيانات الموجودة في هذه الدراسة الحالية ان التغيرات في المعايير الكيميائية - الحياتية والدموية لدى مرضى كوفيد-19 مرتبطة بشكل كبير بخطورة المرض وانتشاره ويمكن استخدامها كعلامات تنبؤية لخطورة المرض.

الكلمات المفتاحية: كوفيد-19, قلة اللبافويات, اختبار البروتين المتفاعل, الفيريتين, دي دايمر, سارس-كوفيد-2.

Introduction

The SARS-COV-2 pandemic began in China in 2019 and spreading through the world. More than 380 individuals around the world have been infected by this virus [1, 2]. Individuals with co-

morbidities such as cardiac vesicular disease, heart disease, diabetic mellitus, kidney, and cancer increased the risk rate of mortality and hospitalization [3]. SARS-COV-2 has multiple variants including alpha, beta, gamma, and delta. The severity of COVID-19 infection varies from one individual to another and organ to another [4].

COVID-19 patients showed changes in biochemical and hematological parameters which may cause other complications [5]. D-dimer is one of the prognostic biomarkers used to predict COVID-19 infection, the elevated level of it considered one of the risk factors for mortality especially in adult COVID-19 patients [6]. D-dimer is one of the fragments released when fibrin cleavage by plasmin to break down clots. A different study demonstrated D-dimer elevated levels associated positively with severe COVID-19 cases [7]. The positive association between D-dimer and disease severity led to the suggested use of D-dimer test as an early marker for severity detection before a CT scan, as well as this marker's association with mortality rate, so used as a single useful biomarker for clinical outcome in COVID-19 patients, and help to identify patients at higher risk for hospital mortality, as well as inform physicians about suitable candidates for intensive care [8].

Another biochemical biomarkers ferritin and CRP. Ferritin is a key mediator of the immune dysregulation via direct immune suppressive and contributing to cytokine storm, especially under the extreme hyperferritinemia condition [9]. This suggested the ferritin level might be considered a crucial factor influencing the severity of COVID-19 [10]. CRP is the first type of acute-phase protein, it is also associated with the propagation of disease and used as a biomarker for monitoring disease progression [11].

SARS-COV-2 has affected the regulation of the immune response through an impaired immune system which includes lymphopenia, monocyte, and granulocyte abnormalities, as well as causes inflammatory immune response through elevated levels of cytokines, especially in COVID-19 critical cases [12]. A decrease in T cell lymphocyte counts which is known as lymphopenia almost observed in severe and critical COVID-19 cases admitted to ICU and is considered the significant predictor factor for disease propagation and poor prognosis [13]. On the other hand, during COVID-19 infection granulocyte number was also affected, in severe cases neutrophils and neutrophils to lymphocytes ratio significantly elevated while the eosinophil and basophile number was reduced [14, 15].

Materials and Methods

This control prospective study case was carried out during the fourth wave of COVID-19. Samples collected through the period (January 2021 to May 2021). Which encompassed (180) individuals of a variety of ages and both sexes, the subjects included (60) individuals who participated

as healthy control RT-PCR COVID-19 negative, and (120) participants were introduced as positive COVID-19 patients were diagnosed by RT-PCR test from nasopharyngeal swabs. The patient's samples were collected from two hospitals in Baghdad which has served as a major Quarantine center in Baghdad which are Dar AL-Salam and Imamein Kadhimein Medical City. All patients were symptomatic with fever, cough, dyspnea, and tiredness. Based on the disease severity the patients were grouped into two groups each of which consisted of (60) patients, which divided into the mild-moderate group and the severe group. Patients were subjected to laboratory tests which included CBC, PCR, and biochemical tests (CRP, ferritin, D-dimer) and oxygen statement, the results were collected from the hospital records system among each patient included in this study. As well as the control group also testy these parameters.

Statistical analysis

Data were analyzed using a statistical package for the social sciences (SPSS version 25, Chicago). The Shapiro-Wilk test was used to detect the normality of data, which revealed the non-normal distribution presented as median, while normal distribution data presented as mean. The chi-squared test used for categorical variables was presented as number and percentage. Mann-Whitney test is one of the non-parametric tests used to detect the significant effect of markers. A value less than 0.05 was considered a statistically significant association.

Results

The median age among the groups studied ranged from (34 to 64) years, with a highly significant association ($p < 0.001$). On the other hand, among the patient groups study 47(39.2%) were male while the females were 73(60.8%), while regarding control group male was 20 (33.3%) and female was 40 (66.7%). Table (1).

Table (1): Demographic characteristic among study groups.

Variables		Groups study			P value
		Control (60)	Mild/moderate (60)	Severe (60)	
Age	Median	34.00	35.00	64.00	<0.001**
	Percentile 05	20.00	19.00	18.00	
	Percentile 95	45.00	73.00	85.00	
Sex	Female	40	35	38	0.638 ^{NS}
		66.7%	58.3%	63.3%	
	Male	20	25	22	
		33.3%	41.7%	36.7%	

P-value ≥ 0.05 statistically non-significant, NS: non-significant

P-value ≤ 0.05 statistically significant, ** statistically high significant at level < 0.001

Biochemical and hematological parameters of COVID-19 patients were performed for all positive COVID-19 patients and control group included in this study by laboratory works by using fully automated biochemistry and fully automated hematology analyzer, then analyzed statistically as shown in (table 2, 3).

Table (2): Biochemical laboratory parameters among study groups.

Variables		Study groups			p. value
		Control	Mild-moderate	Severe	
CRP (mg/L)	Median	2.75	37.50	137.45	<0.001**
	Percentile 05	0.40	19.00	52.60	
	Percentile 95	3.90	112.00	235.00	
Ferritin (ng/ml)	Median	88.50	188.50	209.25	<0.001**
	Percentile 05	41.50	109.50	101.50	
	Percentile 95	149.50	289.50	535.20	
D-dimer (ng/ml)	Median	271.00	1296.50	1539.77	<0.001**
	Percentile 05	173.50	256.50	222.50	
	Percentile 95	415.50	4610.00	7900.00	

Kraskal Wallis test. P-value ≤ 0.05 statistically significant, ** high significant at level <0.001 .

Table (3): Hematological laboratory parameters of study group.

Variables		Study groups			p. value
		Control	Mild-moderate	Severe	
Monocyte %	Median	7.75	9.50	7.85	0.556 ^{NS}
	Percentile 05	6.20	2.90	2.10	
	Percentile 95	9.60	18.30	18.10	
Lymphocyte %	Median	28.30	16.35	13.00	<0.001**
	Percentile 05	23.20	10.25	6.25	
	Percentile 95	35.30	25.25	23.00	
Neutrophil %	Median	53.50	68.00	75.00	<0.001**
	Percentile 05	40.00	56.00	63.50	
	Percentile 95	66.00	76.50	84.00	
Neutrophil/ Lymphocyte	Median	1.85	4.19	6.20	<0.001**
	Percentile 05	1.49	2.59	4.00	
	Percentile 95	2.47	6.50	10.15	

Kraskal Wallis test, NS: non-significant, ** high significant at level 0.001.

Discussion

COVID-19 is considered one of the critical public health problems, it has ramifications for the large number of mortality and morbidity. In this current study, biochemical laboratory parameters reveal the CRP, D-dimer, and ferritin levels among patient groups were in a higher level, compared to the control group; and according to severe group disease were in a higher level

compared to mild-moderate disease with a highly significant association. This finding agrees with different previous Iraqi studies [16, 17] and world studies [18 - 20]. This result can be an illustration of the fact that during COVID-19 infection and response to it the liver synthesizes a high amount of acute phase proteins such as (CRP) [21]. This parameter is highly sensitive to inflammation, infection, and tissue damage [22]. CRP has an essential role in critical and severe respiratory failure and death during SARS-COV-2 infection [18], for this can be used as a prognostic biomarker for early pneumonia diagnosis [23], also high inflammatory cytokines levels in COVID-19 patients such as (IL-6) induced CRP release [24].

On the other hand, the other biochemical parameter D-dimer also reported that patient groups have a higher level than the control group with statistical differences. This agrees with another studies (Tang *et al.*, 2020) in Wuhan, China in 2020 and another study by (Hussein Amer Mohamed Hussein., 2021) in Karbala City during the period extended from October (2020) to February (2021) which reveals the abnormal coagulation function and elevated level of D-dimer associated with severity and poor COVID-19 outcome [25, 26]. Another study also shows that elevated D-dimer level is common in severe COVID-19, it is considered an important reliable prognostic parameter for in-hospital mortality among COVID-19 patients [27]. This finding supported the hypothesis that illustrates that SARS-COV-2 infection causes dysfunction of the hemostatic system and leads to a hypercoagulable state which is most commonly encountered in sepsis cases [28].

Along with other parameters investigated in this current study serum ferritin level was higher in SARS-COV-2 infected patients groups compared with the control group, and higher in the severe group than in mild-moderate group which agrees with the global study (Henry *et al.*, 2020) which found the ferritin level elevated in severe and critical patients group [29]. The ferritin level reflects the stored iron level and also helps in anemia diagnosis. It is elevated during viral infection and is considered an indicator of viral replication [30]. Different studies attributed the elevated level of ferritin during COVID-19 infection to abnormality in immune response and cytokines storm [31, 32]. Likewise, another study (Colafrancesco *et al.*, 2020) found hyperferritinemia syndrome is considered one of the main modifications in COVID-19 infection [33].

In addition, infection with SARS-COV-2 also affected hematological parameters, as shown in this current study monocyte cells in the mild -moderate patients group were higher than in the control and severe group, this result can attributed to disease stage and propagation. the monocyte function is dependent strongly on the local microenvironment and can change in different environments such as oxygen tension, contact with epithelial cells, and the effect of surfactant-rich fluid highlighting the relevance of monocytic plasticity. For this, the monocyte number can be affected by the

treatment course which affects disease stage progression [34]. Likewise, during different viral infections such as Influenza and SARS virus, monocytes are utilized as vessels for viral dissemination, replication, and local for long-term persistence tissues [35]. In contrast other study reveal the monocyte level reduced in COVID-19 patients groups compartment with control and attributed this results to cytokine storm in which occur elevated level of different type of pro-inflammatory cytokines such as IL-6, IL-1 β , also showing Th17 cells producing inflammatory cytokine IL-17 which causes recruit monocyte to the site of infection .There are several limitations present in this study that must be taken into consideration, the small sample size can be considered as one of the most important limitations which may limit the generalization of these results on all Iraqi populations[12].

On the other hand according to the lymphocyte count, the result of this current study also reveal the low counts of lymphocyte cells in severe cases compared with control and mild-moderate cases, this result agree with different studies achievement by (Härter *et al* ., 2020 and Tavakolpour *et al* ., 2020) who explain the most important criteria during COVID-19 was low of lymphocytes counts which known (lymphopenia) especially in severe and critical COVID-19 patients, and attributed this to inflammatory cytokine storm such as (IL-6, TNF- α) which have closely correlated with lymphopenia [36, 37] . Different mechanisms also can illustrate lymphopenia criteria which included, during COVID-19 infection T-cells were infected directly by virus due to the expression of ACE2 on lymphocyte cells which allowed entry into it [38, 39] in severe cases elevated levels of inflammatory cytokines which correlated inversely with lymphocytes and affected negatively on survival and proliferation of them, also causes exhaustion of T-cell population [40]. SARS-COV-2 has the ability to directly destroy and damage the lymphatic organs spleen and lymph nodes. Moreover, in severe COVID-19 cases the lactic acid level increases in the bloodstream which also can cause inhibitory lymphocyte proliferation which ultimately causes lymphopenia [41, 42].

Moreover, severe cases also reveal significantly elevated levels of Neutrophils over mild-moderate and control cases with high statistical differences, in addition the current study results reveal significant differences among Neutrophil / Lymphocyte (NLR) in severe patients. The elevated level of neutrophil count reveals the intensity of the inflammatory system whereas lymphopenia reflects sequestration and apoptosis of lymphocytes in the inflammation site.

The combination of these two biomarkers (NLR) may improve the prediction of disease progression statements [43, 38].

NLR indicated the critical and severe infected cases and serious disturbance of the internal environment. It has been also used as a predictor marker of bacterial infection due to a dysregulated immune system in SARS-COV-2 infection [20].

Conclusion

Overall, COVID-19 affected the Hematological and biochemical parameters level dependent on the disease stage.

- 1- Data present in this current study reveal the alterations among biochemical parameters CRP, ferritin, and D-dimer in COVID-19 patients correlated significantly with disease severity and propagation.
- 2- These parameters used as prognostic predictive markers for disease severity.
- 3- As well as the current study results confirm the positive correlation between NLR and disease propagation which improves the possibility of utilizing this ratio as a severity prognostic index.
- 4- Lymphopenia is one of the most important hematological indicators of disease severity.
- 5- Therefore, early application of these parameters is thought to benefit the physicians to take early management steps and alter the management plan of the clinical course for COVID-19 patients.

Recommendations

To obtain comprehensive results and better understand the effects of COVID-19 on hematological and biochemical markers recommended take a larger sample size from different regions of the country.

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