STUDY OF HEMATOLOGICAL PARAMETERS IN PATIENTS WITH COVID-19 DISEASE IN KURDISTAN REGION-IRAQ

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ABSTRACT

Background: Coronavirus disease 2019 is an infectious disease that was found at the end of 2019. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recognized as the virus that leads to COVID-19. The study was directed to find out the hematological parameter changes in COVID-19 patients according to the severity of the disease.

Methods: The study has been done in two centers Sulaymaniyah and Duhok Governorates for a period of six months between September 2021 to March 2022. A total of 201 enrolled patients were included. For each patient demographic characteristics and blood test results (total and differential WBC, Hb, platelet, ferritin, CRP, D-dimer, NLR, PLR) were collected, following the severity of the disease and the outcome of each one of the patients. SPSS software was used for statistical analysis.

Results: The study revealed that female patients were more than males 60.2% and 39.8% respectively with an overall mean age of 54.65±17 years. The mean duration of hospitalization is 14.4 ± 7.7 days. Furthermore, the study showed that patients had 30.8% leukocytosis,17.4% lymphopenia, and 31.8% neutrophilia. Higher NLR and PLT are seen in severe cases with NLR ≥3.1and PLR ≥ 285. Also, high levels of CRP, D-dimer, and ferritin were seen in severe COVID-19 patients.

Conclusions: Changes in hematological parameters can be useful in predicting of the disease severity of COVID-19 patients.

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Keywords: *COVID-19, hematological parameters, leukocytosis, lymphopenia, neutrophilia, NLR, PLR.*

One of the important animal and human pathogens is coronaviruses. COVID-19 was pointed out at the end of 2019, in Wuhan city in Hubei province of China as the cause of infectious disease in some groups of patients. The virus spread quickly, which was causing an epidemic all over China, then followed by a huge number of patients worldwide[1]. The virus is a (single-stranded RNA virus) that originated from the beta Coronavirus family. The World Health Organization (WHO) in February 2020 named the disease COVID-19, which stands for coronavirus disease 2019, which was caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2].

The worldwide COVID-19 disease impends all countries' biosecurity including Kurdistan Region-Iraq. The first case of the virus was confirmed and stated on March 1, 2020, in Sulaymaniyah Governorate. Still the virus is spreading, which is carrying a serious health problem to the population[3].

To prevent unfavorable outcomes in patients with COVID-19 starting early identification and treatment are very

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important4. Thus, abnormal hematological parameters in COVID-19 patients can help in the earlier beginning and prognostication of the risk patients.

So, the monitoring the changes in hematological parameters like (WBC count, lymphocyte, neutrophil, platelet, hemoglobin, and D-dimer)[4,5], and also mostly severe patients had high levels of infection-related biomarkers and inflammatory cytokines such as ferritin and CRP presenting in COVID-19 patients[6].

Relations between blood cells are important in the pathophysiology of hemostasis, inflammation, oncogenesis, and immune responses. Several studies revealed that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are inflammatory markers of immune-mediated, neoplastic diseases, prothrombotic, and metabolic, which are commonly examined like an essential prognosticator for prognosis in so many different disorders[7].

The objective of the study was to reveal the abnormal hematological parameter in Kurdistan patients and to select those parameters that could aid in distinguishing patients expected to develop severe COVID-19 disease.

PATIENTS AND METHODS

It was a cross-sectional multicenter study, obtaining ethical approval from the Research Ethics Committee and Ministry of Health in Kurdistan Region-Iraq (Date:15,September, 2021, Reference number: 15092021-9-18). The period of the study was six months between September 2021 to March 2022. The sample and data of the patients with COVID-19 were obtained from Sulaymaniyah and Duhok Governorates. 201 enrolled patients were involved from both sexes. Those patients which had hematological diseases and those under chemotherapy treatment were not included. Pregnant women and children and also patients less than 18 years of age were not included. All the patients were confirmed by positive test results for COVID-19 by using (Roche- LightCycler 96)and(Qiagen kit for RNA extraction and proliferation) for analysis of real-time polymerase chain reaction (RT-PCR) based on the WHO standards for having positive results for nasopharyngeal swab specimens.

All patients' hematologic parameters (total and differential WBC, Hb, platelet, ferritin, CRP, D-dimer, NLR, PLR) and demographic characteristics were recorded with the patients' history. All patients are classified according to the severity of the disease depending on the WHO classification of (mild, moderate, and severe)8. All of them were treated (either as an inpatient or as an outpatient with various degrees of illness). The length of hospitalization was reported for all patients. The study outcomes were improvement or death.

STATISTICAL ANALYSES

Data were collected and coded. The collected data got analyzed and reviewed by using the Statistical Package for Social Sciences (SPSS version 22). Descriptive statistics like percentage and frequency got calculated. Measures of central tendency and dispersion around the mean were used to describe continuous variables. P-value was obtained for categorical variable chi-squarepoc testing) and was considered significant if it was less than 0.05.

RESULTS

The demographic characteristics of patients shown in table 1, as showed that females (60.2%) were more than males

(39.8%) with an overall mean age of 54.65±17.3 years. The admission place of the patients according to the disease severity was categorized into three different groups.

The hospitalization period ranged from 3 to 41 days with a mean duration of hospital stay of 14.4 ± 7.7.

Table 1: Demographic characteristics of COVID-19 patients.

Variables	(n = 201)	(n= %)	(Mean ±SD)
Age group			54.65±17.3
18 – 45	65	32.3	
46 – 65	78	38.8	
> 65	58	28.9	
Gender			
Male	80	39.8	
Female	121	60.2	
Place of Admission			
Not hospitalized	61	30.3	
Ward	80	39.8	
ICU	60	29.9	
Length of hospitalization			14.4 ± 7.7
≤ 14 days	84	60.0	
> 14 days	56	40.0	

The hematological parameters frequencies shown in table 2, as shown that in a total of 201 patients, anemia was present in 28.9% of them who mostly had moderate and severe.

Lymphopenia was seen in 17.4% of the cases who almost had moderate and severe disease, the other 82.1% of cases had a normal number of lymphocytes which is statistically significant <0.001.

Neutrophilia was present in 31.8% of patients with moderate and severe diseases compared to the other 66.2% who had a normal number of neutrophils.

High level of ferritin seen in 93% of the patients, which was most of them had moderate and severe disease compared to other 7% which had normal ferritin levels which is almost all patients had the disease.

C-reactive protein CRP level was high in 81.1% of patients, which mostly they had moderate and severe disease as compared to other 18.9% with normal CRP levels which is most of the patients had the disease.

The D-dimer level was high in 77.1% of patients, which mostly they had moderate and serious disease compared to other 22.9% with normal D-dimer levels which is most of the patients had the disease.

Table 2: The hematological parameters frequencies of COVID-19 patients in relation to the severity degree.

Variables	Total	Severity of disease			*P*
		Mild	Moderate	Severe	
Hb					0.16
Anemia	58(28.9)	11(18.0)	28(35.0)	19(31.7)	
Normal	143(71.1)	50(82)	52(65)	41(68.3)	
WBC					<0.001
Leukopenia	8(4.0)	3(4.9)	4(5.0)	1(1.7)	
Normal	131(65.2)	55(90.2)	47(58.8)	29(48.3)	
Leukocytosis	62(30.8)	3(4.9)	29(36.3)	30(50.0)	
Lymphocyte					<0.001
Lymphopenia	35(17.4)	1(1.6)	23(28.7)	11(18.3)	

Normal	165(82.1)	60(98.4)	57(71.3)	48(80.0)	
Lymphocytosis	1(0.5)	0(0.0)	0(0.0)	1(1.7)	
Monocyte					<0.001
Monocytopenia	15(7.5)	0(0.0)	13(16.3)	2(3.3)	
Normal	178(88.6)	60(98.4)	64(80.0)	54(90.0)	
Monocytosis	8(4.0)	1(1.6)	3(3.8)	4(6.7)	
Neutrophil					<0.001
Neutropenia	4(2.0)	2(3.3)	2(2.5)	0(0.0)	
Normal	133(66.2)	56(91.8)	47(58.8)	30(50.0)	
Neutrophilia	64(31.8)	3(4.9)	31(38.8)	30(50.0)	
Platelet					0.99
Thrombocytopenia	6(3.0)	2(3.3)	2(2.5)	2(3.3)	
Normal	180(89.6)	55(90.2)	71(88.8)	54(90.0)	
Thrombocytosis	15(7.5)	4(6.6)	7(8.8)	4(6.7)	
Ferritin					<0.001
Normal	14(7.0)	13(21.3)	1(1.3)	0(0.0)	
High	187(93.0)	48(78.7)	79(98.8)	60(100.0)	
CRP					<0.001
Normal	38(18.9)	33(54.1)	2(2.5)	3(5.0)	
High	163(81.1)	28(45.9)	78(97.5)	57(95.0)	
D- dimer					<0.001
Normal	46(22.9)	32(52.5)	10(12.5)	4(6.7)	
High	155(77.1)	29(47.5)	70(87.5)	56(93.3)	
Total	**201(100.0)**	**61(100.0)**	**80(100.0)**	**60(100.0)**	

Neutrophil/lymphocyte ratio was high ≥ 3.1 in 67 patients (33.3%) most of them 48(78.7%) had severe disease, while only 10(16.7%) of the patients had mild disease. Low NLR <3.1was seen in 134 patients (66.7%) and only 12(21.3%) of the patients had a serious disease which is statistically significant <0.001 as shown in table 3.

Table 3: The severity degree of COVID-19 patients in relation to NLR

Variable		severity degree				
		Total	**Severe**	**Moderate**	**Mild**	**P-value**
Neutrophil/lymphocyte ratio %	≥3.1	67(33.3)	48(78.7)	9(11.3)	10(16.7)	<0.001
	<3.1	134(66.7)	12(21.3)	71(88.8)	51(83.3)	
Total		**201(100.0)**	**60(100.0)**	**80(100.0)**	**61(100.0)**	

The Platelet/lymphocyte ratio in this study showed a high PLR ≥ 285 was found in 89 patients, and only 7 of the patients had a mild disease compared to the other 112 patients with PLR≤172, which is 54 of them had the mild disease (P=<0.001) as shown in table 4.

Table 4: The severity degree of COVID-19 patients in relation to PLR

Severity of disease	Platelet/lymphocyte ratio		Total	P-value
	≤172	≥ 285		
Severe	23(20.5)	37(41.6)	60(29.9)	<0.001
Moderate	35(31.3)	45(50.6)	80(39.8)	
Mild	54(48.2)	7(7.9)	61(30.3)	
Total	**112(100.0)**	**89(100.0)**	**201(100.0)**	

Of the total of 140 patients who were hospitalized in the wards and ICU, 19 of them had high NLR (≥3.1); 12 of them stayed in the hospital for ≤ 14 days, and the other 7 patients for > 14 days. 121 of the patients with low NLR (<3.1); 72 of them stayed in the hospital for ≤ 14 days, and the other 49 patients for > 14 days as in table 5.

Table 5: NLR in COVID-19 patients in relation to the length of hospitalization.

Neutrophil/lymphocyte ratio %	Length of hospitalization			P-value
	Total	≤ 14 days	> 14 days	
≥3.1	19(100.0)	12(63.2)	7(36.8)	0.8
<3.1	121(100.0)	72(59.5)	49(40.5)	
Total	**140(100.0)**	**84(60.0)**	**56(40.0)**	

of the total of 140 patients who were hospitalized, 56 of them had a longer duration in hospital (>14 days) which was 37 of them had PLR ≥ 285, while only 19 of the patients had ≤172 as shown in table 6.

Table 6: PLR in COVID-19 patients in relation to the length of hospitalization.

Platelet/lymphocyte ratio	Length of hospitalization		Total	P-value
	≤ 14 days	> 14 days		
≤172	39(67.2)	19(32.8)	58(100.0)	0.16
≥ 285	45(54.9)	37(45.1)	82(100.0)	
Total	**84(60.0)**	**56(40.0)**	**140(100.0)**	

DISCUSSION

The COVID-19 disease causes serious health problems all around the world. Determining the hematological abnormalities in COVID-19 patients is essential and useful for the early identification and treatment, also increasing efforts to control or reduce virus transmission. This study includes 201 patients with COVID-19 disease with confirmed positive RT-PCR from both Sulaymaniyah and Duhok governorates.

This study showed that females were more affected than males with an overall mean age of (54.65±17) years which parallels a study bout COVID19 epidemiology in Basra -Southern Iraq[9].

The elevated leukocyte count was mostly seen in patients with severe disease compared to those who had mild disease10. The study shows that leukocytosis found in (30.8%) was mostly associated with moderate to severe disease. Lymphopenia was found in (17.4%) of patients with moderate and severe disease. It is one of the most frequently recorded hematological abnormalities in COVID-19[10,11,12], those patients had low lymphocyte count; the state that is connected to the disease severity and outcome of COVID-19 patients[13]. It was also detected in some other Asian studies; however, the studied population data showed a smaller percentage as compared to 63% from Wuhan, and 42% of patients outside Wuhan[14,15]. Therefore, COVID-19 patients that died were recognized to have lower lymphocyte counts than those patients who survived[16].

One of the most important clinical findings in those patients who need ICU is fulminant neutrophilia[17,18]. Those patients who were stay in the ICU has high neutrophil counts in their blood as compared to other patients with less severe disease[17]. In our study neutrophilia was found in (31.8%) of patients with moderate and severe diseases which is significant.

Thrombocytopenia was found in only (3.0%) of the patients. Therefore, in this study low platelet count was not linked to the severity of the disease, something which did not parallel to the results of the meta-analysis of Giuseppe Lippi et al. [9,19].

A high level of D-dimer was found in (77.1%) of patients, and mostly they had moderate and severe disease. It is one of the important laboratory tests that is required for the diagnosis of COVID-19 patients[20]. D-dimers seem to be the most valuable coagulation parameter as a progressive increase in D-Dimer level is connected with severe disease development. So, sequential monitoring of it could be a valuable biomarker of clinical severity in COVID-19[21]. A high level of D-dimer may be caused by inflammation related to COVID-19 disease and following coagulation activation. Numerous potential risk factors during hospital staying duration, like disseminated intravascular coagulation, dehydration, infection, prolonged immobilization, mechanical ventilation, and central venous catheter use may further increase D-dimer level[22]. Since thrombosis can happen in several organs and following organ failure in severe cases of COVID-19, so D-dimer monitoring can be a critical approach in the clinical practice of COVID-19 infection[20].

A high serum ferritin value was seen in (93%) of the patients and a normal serum ferritin value was seen only in (7%) of them almost they had mild disease, while almost all patients with moderate and severe disease had high serum ferritin levels. This result is matching to a published study by vergas-vergas[23]. Zhou et al revealed that the increase in ferritin levels is related to the worsening of the COVID-19[24]. In this study, severe cases had higher ferritin levels as compared with the levels in less severe patients. The ferritin concentration is increased in those with a high mortality risk, and decreasing the level shows the control of inflammation as well as promoting survival [25,26].

C-reactive protein CRP level was high in 81.1% of the patients, which mostly they had moderate and severe disease, these results are parallel to the Second Affiliated Hospital of Wenzhou Medical University study which shows that higher levels of CRP designated severe COVID-19 disease and longer hospitalization period[27].

Clinicians are trying and searching for a dependable prognostic marker that could aid in distinguishing those patients in danger of developing the more severe disease. The NLR in peripheral blood has been studied as a systemic inflammatory marker, and numerous researches had revealed that it is an effective prognostic factor in many solid tumors[28] and other long-term diseases like (cardiovascular, lung, and renal diseases)9. High NLR can be an early prognostic marker in COVID-19 diseases[29], and it increased mostly in severe patients when compared to non-severe COVID-19 patients11.

In this study, we calculated the NLR in relation to the hospitalization duration and outcome of the disease and showed that (33.3%) of the patients with an NLR ≥3.1, and most of them (78.7%) had severe disease category (P = <0.001), and (36.8%) of them had a long duration of hospitalization (>14 days). Our results were parallel with those of Yang et al. studies about the relationship between NLR and the detection of various infectious diseases[30]. Moreover, the study found that 89/201 patients had higher PLR, mostly they had moderate and severe disease only 7 of them had mild disease P=<0.001, and (45.1%) of them had a long duration of hospitalization (>14 days).

The outcome of this study revealed that most frequent hematological abnormalities in COVID-19 patients were lymphopenia, leukocytosis, neutrophilia, anemia, and high values of both NLR and PLR are significantly linked with the severity of the disease. Monitoring of hematological parameters can be useful in differentiating severe versus non-severe disease, also management and risk stratification of the patients with COVID-19.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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پوختە

توێژینەوەی پێوەرەکانی خوێن لە نەخۆشانی تووشبوو بە نەخۆشی COVID-19 لە هەرێمی کوردستان

پێشەکی و ئارمانج: نەخۆشی کۆرۆنا ٢٠١٩ نەخۆشییەکی درمییە کە لە کۆتایی ساڵی ٢٠١٩ دۆزرایەوە، لە شاری وهان لە پارێزگای هوبێی چین. ئەمە ڤایرۆسێکی RNA تاکە ڕیشاڵییە کە لە بنەماڵەی Beta Coronavirus سەرچاوەی گرتووە. نەخۆشی توندی هەناسەدان ڤایرۆسی کۆرۆنا 2 (SARS-CoV-2) وەک ئەو ڤایرۆسە ناسێندرا کە دەبێتە هۆی COVID-19. چەندین گۆڕانکاری لە پارامێتری خوێن لە نەخۆشەکاندا دەستنیشان کران. توێژینەوەکە ئاڕاستەکراوە بۆ زانینی گۆڕانکارییەکانی پارامێتری خوێن لە نەخۆشانی کۆڤید ١٩ بەپێی توندی نەخۆشییەکە و دەرئەنجامەکەی.

شێوازەکان: توێژینەوەکە لە دوو سەنتەری پارێزگای سلێمانی و دهۆک بۆ ماوەی شەش مانگ لە نێوان مانگی ئەیلولی ٢٠٢١ تا ئازاری ٢٠٢٢ ئەنجامدراوە، بە گشتی ٢٠١ نەخۆشی ناونوسکراو بەشداربوون. بۆ هەر نەخۆشێک تایبەتمەندی دیمۆگرافی و ئەنجامی پشکنینی خوێن کۆکرایەوە، بەدواداچوون بۆ توندی نەخۆشییەکە و دەرئەنجامی هەر یەکێک لە نەخۆشەکان. بۆ شیکاری ئاماری سۆفتوێری SPSS بەکارهات.

ئەنجام: توێژینەوەکە دەریخست کە نەخۆشانی مێینە زیاتر لە نێرەکان ٦٠,٢٪ و ٣٩,٨٪ بوون بە تێکڕای تەمەنی گشتی ١٧±٥٤,٦٥ ساڵ. تێکڕای ماوەی خەواندن لە نەخۆشخانە ٧,٧ ± ١٤,٤ ڕۆژە. جگە لەوەش، توێژینەوەکە دەریخستووە کە نەخۆشەکان ٣٠,٨٪ لیکۆسایتۆزی و ١٧,٤٪ کەمبوونەوەی لیمفۆ و ٣١,٨٪ نیوترۆفیلیایان هەبووە. NLRلەم توێژینەوەیەدا (٢٠١/٦٧) نەخۆشی نیشان دا کە٣,١≤ NLR یان هەبوو. هەروەها، ٢٨٥≤ PLR لە (٢٠١/٨٩) لە نەخۆشەکاندا دۆزرایەوە.

دەرەنجامەکان: گۆڕانکاری لە پێوەرەکانی خوێندا دەتوانێت سوودبەخش بێت لە پێشبینیکردنی توندی نەخۆشییەکە و دەرئەنجامی نەخۆشانی کۆڤید ١٩.

الخلاصة

دراسة عن قياسات معلمات الدم عند المرضى المصابين بمرض كوفيد -19 في إقليم كوردستان-العراق

الخلفية والأهداف: مرض كورونا (فايروس كوفيد 2019) هو مرض معدي ظهرت في نهاية عام 2019 في مدينة وهان ضمن مقاطعة هوبي الصينية. هذا الفايروس هو أحادي سلاسل فايروس RNA طورت من عائلة بيتا فايروس التاجي. متزامنة جهاز تنفسي الحاد الشديد فايروس تاجي 2 (SARS –Cov_2) سببها هو هذا الفايروس ويؤدي الى كوفيد 19. هنالك كثير من العدادات قياس مكونات الدم تتغير عند ظهور وتشخيص المرض عند المصاب. من خلال هذه الدراسة نحاول أن نجد هذه التغيرات عند المصابين بـ(كوفيد 19) وعلاقته بشدة الاصابة ونتيجة الحالة بعد الاصابة.

طرق العمل: الدراسة أجريت في مركزين منفصلين في محافظتي دهوك والسليمانية من خلال ستة أشهر ابتداءاً من أيلول 2021 الى مارس 2022. وعدد المرضى المسجلة في الدراسة 201 ولكل مريض أخذت منه المعلومات العامة والفحوصات المطلوبة وتابعت الحالة من حيث شدة الحالة المرضية والنتجية النهائية لحالته. واستخدمت سوفت SPSS للتحليل الاحصائي.

النتائج: بينت من خلال الدراسة وذلك بأن نسبة ألاناث أكثر من الذكور 60.2% و 39.8% على التوالي ومعدل العمر 54.65±17 سنة. ومعدل المدة البقاء في المستشفى هو 7.7 ±14.4 يوم. وكذلك من خلال هذة الدراسة بينت لنا بأن 30.8% من الحالات هنالك زيادة في كريات الدم البيض, 17.4% قلة خلايا المفاوية و13.8% زيادة في كريات الدم البيض العدلة. NLR في الدراسة (67/201) من المرضى و3.1 < NLR كذلك. 285 < PLRوجدت في (89/201) من المرضى.

الاستنتاجات: تغيرات في القياسات كريات الدم مهمة في نتيجة المرض كورونا وكذلك في تحديد شدة خطورة المرض.