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Hematological changes among Corona virus -19 patients: a longitudinal study

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ABSTRACT

COVID-19 is an aggressive virus spread worldwide and caused pandemic infection and there is an urgent need to identify a predictor whether clinical or laboratory. Now the challenged against coronavirus disease 2019 (COVID-19), not only to the diagnosed virus but to predict the progression towards severe and fatal forms, these predictors will enable risk stratification, guide interventional studies to target patients at enhanced risk of developing severe disease and optimize the allocation of limited human and technical resources in the ongoing pandemic. Moreover, identification of laboratory parameters capable of discriminating between severe and non-severe cases, or those at high or low risk of mortality, will allow for improved clinical situational awareness. The present study sheds the light on the role of three hematological markers (hemoglobin, weight blood cell & platelets) each one of them has a role in the development of signs and symptoms. So, this longitudinal study is designed to investigate the effect of three hematological markers on the prognosis of the disease .Blood samples were collected from 296 newly diagnosed patients with COVID19 at Al-Hakeem of a local hospital in Najaf-Iraq from March 1th to April 23rd, 2020. The results show, the mean of three hematological markers significantly increased with a mild sign (P =0.005, 0.002&0.005) for hemoglobin, WBC &platelets respectively. Moreover, by using the Kaplan-Mier test the mortality rate of COVID-19 patients increased with low levels of three hematological marker concentration during a maximum of 4weeks of follow up periods post-diagnosis. By using a ROC curve the three hematological markers shows a good test to predict patients with severe cases. From these findings, we can conclude that high expression of platelets, hemoglobin, and WBC (weight blood cell) correlates with the surviving rate and .may be used as the prognostic marker

Keywords: Hematological changes, Corona virus -19

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INTRODUCTION

Coronaviruses are a large group of viruses known to cause illnesses that vary between colds and more severe diseases, such as Middle Eastern Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS) [1]. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China [2]. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. This virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV [3].The infection is usually transmitted from person to person with respiratory droplets caused by coughing or sneezing. The time between exposure to the virus and the onset of symptoms ranges from 2 to 14 days, with an average of five days [4]. The standard diagnostic method is a Real-time polymer chain reaction (RT-PCR) on a smear taken from the nasopharynx, throat, and sputum [5-6]. Infection can also be diagnosed by combining symptoms and risk factors with computerized tomography (CT-SCAN) of the chest that shows signs of pneumonia. Measures to prevent infection include frequent hand-washing and social exclusion (maintaining adequate distance between individuals) and avoiding touching the face [7]. Medical masks are recommended for those suspected of carrying the virus and for the people caring for them, while the common people are not advised to wear them. There is still no effective vaccine or viral treatment against COVID-19, and measure efforts are focused on symptomatic treatment, support for vital functions, isolation, and experimental measures [8]. In IRAQ 24/FEB/2020 the first diagnosed of COVID-19 in Najaf city, the patient is a student of religion who came from Iran to study in Iraq, In 25/FEB/2020 Iraq recorded four patient's in Kirkuk city all they came from Iran, after that the numbers started to increase in some governorates (Baghdad, Babylon, Sulaimanya, Maysan), That leads to speared the virus this prompted the government to announce a curfew in all governorates [9]. The Najaf has an isolation hospital called AL-Hakeem, in addition to that The Najaf Health Department with a donation from some institution it provided five other places for isolation infected people, the numbers of patients until 1/4/2020 in Najaf is 122 infected, the recovering numbers is 31 patients and the deaths numbers is (4) patients(9)The purpose of this research to know hematological changes among patients with COVID-19 [10].

METHOD AND PATIENTS

Study Design

This prospective longitudinal study was conducted at Al-Hakeem of a local hospital in Najaf-Iraq fromMarch1th to

April 23rd, 2020 after obtaining ethical approval from the Najaf governorate health sector/Iraq. A total of 296 patients included in the study were those in whom with criteria diagnosis of COVID-19 by using PCR with respiratory clinical symptoms and sign had been confirmed by Baghdad central laboratory. Blood samples were collected by vein puncture 5 milliliter (ml) of venous blood withdrawn from COVID19 by using disposable syringes under aseptic technique; they then transferred to 10 ml sterile EDTA tube, for complete blood count.

Statistic

Data were translated into a computerized database structure. An expert statistical advice was sought for. Statistical analyses were computer-assisted using SPSS version 24 (Statistical Package for Social Sciences). Frequency distribution for selected variables was done first. Horizontal bars indicate the means. For multiple comparisons, *p* values will be calculated by a one-way ANOVA. The Kaplan-Meier estimate is the simplest way of computing survival over time despite three haematological markers associated with disease prognosis. A receiver operating characteristic (ROC), or simply ROC curve, is a graphical plot and it is created by plotting the fraction of true positives (sensitivity) out of the positives *versus* the fraction of false positives (specificity) out of the negatives, at various threshold settings. $P < 0.05$ was considered statistically significant.

Result

Table (1) shows the division of ages from the youngest age (11-20) to the oldest age(71-80 years) at the date from March1th to April23rd, 2020

Age group	*N.*	Percent
11-20	34	11.5
21-30	74	25.0
31-40	86	29.1
41-50	46	15.5
51-60	26	8.8
61-70	20	6.8
71-80	10	3.4
Total	296	100.0

N: Number

It was noted that the largest number of those who were infected between the ages of (31y-40y).

Table (2): show clinical-pathological feature

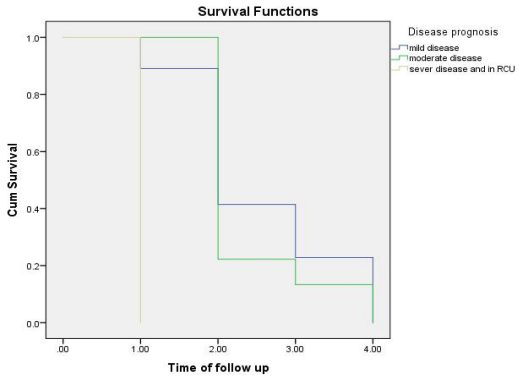
Pathological feature	*N*	Percent%
mild disease	212	71.6
moderate disease	52	17.6
sever disease and in RCU	32	10.8
Total	296	100.0

The high expression of three hematological markers had a positive correlation with the surviving rate during four weeks as shown in table (3) and figure (1). Mean of surviving rate among time significantly increase(2.547, 2.533&2.587) with a high concentration of three hematological marker((10.5 to12)g/L, ≥(10.000) * 10 million/µL&≥140 *10-3/µL) for hemoglobin, white blood cell & platelets level respectively compared with a mean (1.429, 1.636&1.636) of low concentration (≤(7 to 8)g/L, ≤(4.000-6.000) * 10 million/µL&≤(80-100 *10-3/µL)for hemoglobin, white blood cell & platelets level respectively. P = 0.005, 0.002&0.005 for hemoglobin, WBC & platelets respectively. The same thing occurs with the pathological feature when patients come with a mild sign and symptom the probability of surviving and healing increase (2.521) compared with patients who suffer from severe respiratory tract infection and pneumonia and translocated in RCU unite (1.000) where dying increased as appears in, Table 3 and Figure 1, (P=0.001).

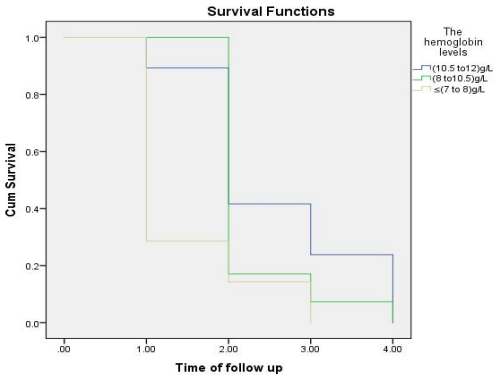
Table (3): Kaplan-Mier Survival Showing the Cumulative Survival and Death Estimates (in Addition to Mean Survival Time) During a Maximum of 4 Week Follow up Period by disease prognosis and three hematological marker categories

	Mean		95% Confidence Interval		*P**
Disease prognosis	Estimate	Std. Error	Lower Bound	Upper Bound	0.001
mild disease	2.521	.067	2.403	2.664	
moderate disease	2.356	.106	2.147	2.564	
sever disease and in RCU**	1.000	.000	1.000	1.000	
Overall	2.462	.058	2.347	2.576	
The hemoglobin levels					0.00
(10.5 to12)g/L	2.547	.066	2.417	2.677	
(8 to10.5)g/L	2.244	.091	2.066	2.422	
≤(7 to 8)g/L	1.429	.297	.846	2.011	
Total	2.469	.058	2.356	2.583	
The WBC*** con.					0.002
≥(10.000) * 10 million / µL	2.533	0.069	2.397	2.669	
(7.000-10.000) * 10 million / µL	2.407	0.107	2.197	2.618	
≤(4.000-6.000) * 10 million / µL	1.636	.152	1.338	1.935	
Total	1.682	.043	1.597	1.767	0.00
The Platelets con****.					0.00
≥(140 *10-3/µL)	2.587	.071	2.447	2.726	
(100-130 *10-3/µL)	2.218	.081	2.060	2.377	
≤(80-100 *10-3/µL)	1.636	.152	1.338	1.935	
Total	2.469	.058	2.356	2.583	

a. Estimation is limited to the largest survival time if it is censored- Value <0.05,** Respiratory Care Unite, ***Wight Blood Cell



(A)



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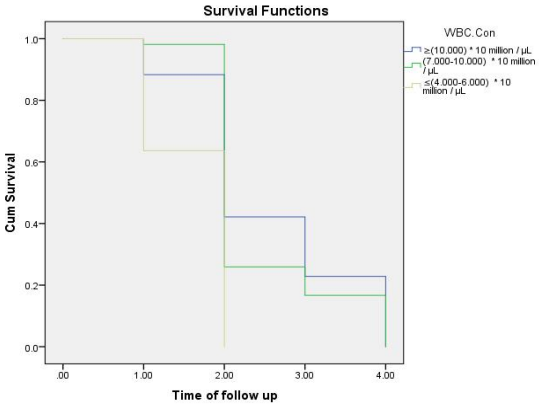

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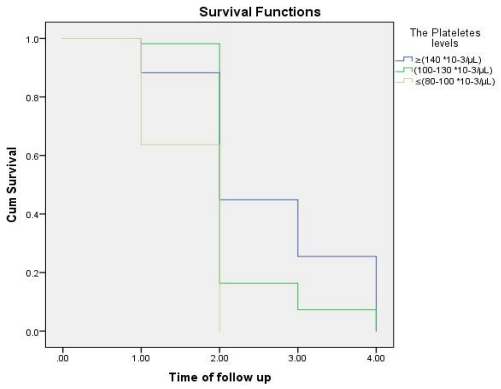


(D)

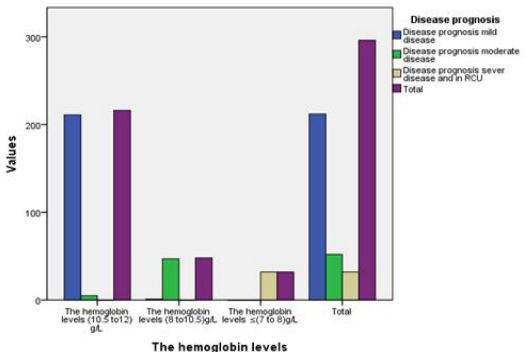
Figure (1):A Survival Curve(Kaplan merrier carve) Comparing the Cumulative Survival Rates During 4 weeks of Follow up for Cases With COVID-19 by A: disease prognosis B: hemoglobin con, C: disease prognosis, D: the platelets level D:WBC concentration

Table (4): Log Rank (Mantel-Cox) table shows the Test of equality of survival distributions for the different levels of the Disease prognosis and three hematological markers

Log Rank (Mantel-Cox)	Chi-Square	df	*P* Sig.
Disease prognosis	56.664	2	.001
The hemoglobin levels	19.508	2	.005
The WBC con.	12.943	2	.002
The platelets con.	19.564	2	.005

P-Value <0.05;sig:significant.

To show the association between study hematological variables and pathological features all three stations of measurements (baseline, after first, second, third, and fourth weeks) were aggregated together. As shown in figure (2: D,E&F) the mean of three hematological markers significantly increased in mild disease compared with severe respiratory tract disease and RCU unit, *P*=0.001,0.001&0.005 for hemoglobin, WBC & platelets respectively. The highest concentration of hemoglobin level seen in the first week of administration then the level significantly decreased in the second,third, and fourth week of followup in sever cases, *P*<0.008. Figure (2: A). Meanwhile, the level WBC & platelets was decreased but as statistically nonsignificant with the time of fellowup, *P*<0.022& 0.81 for WBC & platelets respectively, Figure (2: B&C).All three quantitative hematological measurements were tested for their ability to predict a severe disease of COVID 19 patients. All of them provided a good test in this context (ROC area ≥ 0.6). the platelets were the best among the three, while WBC concentration was the least valid,then hemoglobin as in Table (5) and Figures (3)



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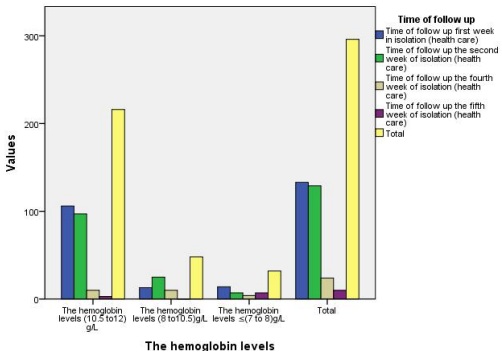

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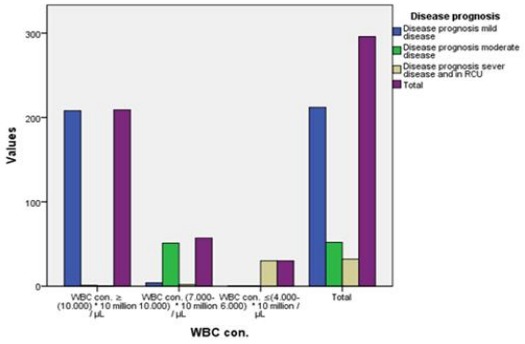

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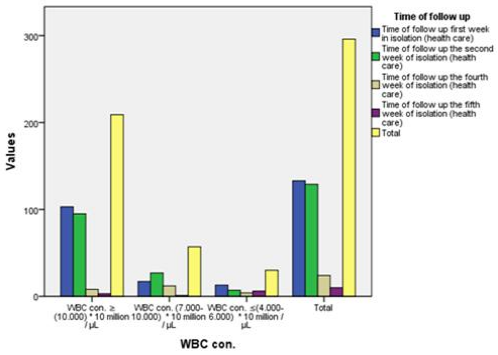

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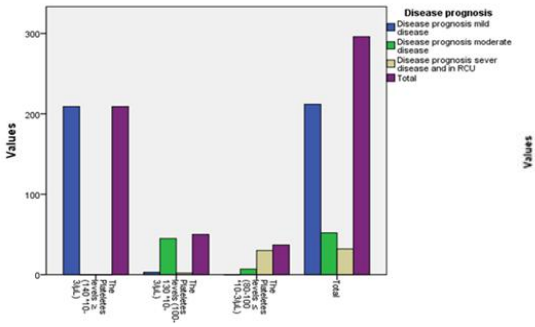

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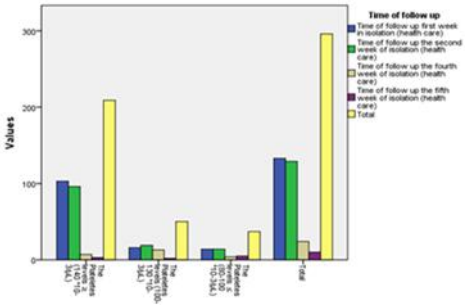

D

Figure(2):changes in means of a hematological marker according to disease prognosis and time of follow-up

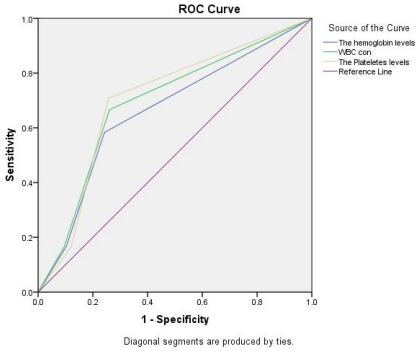

Figure (3): A ROC Curve Showing the Trade-off between Sensitivity (Rate of True Positive test Results) and 1-Specificity (Rate of False-Positive Test Results)

Table (5): The Area under ROC Curve For three hematological markers When Used as a Test to Predict Cases with severe respiratory tract infection by COVID-19

Area Under the Curve		
Test Result Variable(s)	ROC Area	*P*
The hemoglobin levels	0.661	≤0.001
WBC con	0.693	≤0.001
The Platelets levels	0.704	≤0.001

DISCUSSION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), was first reported in Wuhan, Hubei province, China has now rapidly spread over 50 countries. For the prevention and control of infection, Taiwan Centers for Disease Control initiated testing of SARS-CoV-2 on January 24th, 2020 for persons suspected with this disease [11], In comparison with patients in the early phase of COVID-19 illness. Therefore, contact and travel history are the main screening criteria for SARS-CoV-2. The development of mild COVID-19 illness was insidiously initiated and persisted for a long period. The prolonged duration of SARS-CoV-2 detection in or pharyngeal specimens of the COVID-19 patients with mild illness is of concern in epidemic areas. The data of this study showed obvious relation between low hemoglobin level and outcome of COVID-19 in prognosis and recovery which is a convent with other studies, that explain hemoglobin value was found to be significantly lower in COVID-19 patients with the severe disease than in those with milder forms, yielding a weighted mean difference of −7.1 g/L, with a 95% confidence interval of −8.3 g/L to −5.9 g/L. On the other hand; the results of this study strongly showed that the worse prognosis of COVID-19 patients associated with a low level of platelet count and Patients with the level of platelet ≤100 is more subjected to admit in the respiratory care unit with pneumonia and respiratory distress syndrome. Furthermore; platelet more than $150x10^9$ have a good recovery and decrease daily admitted in hospital and less complication with limited use of antibiotics and supportive treatment, and this resulted data convenient with other paper research that showed thrombocytopenia is common in patients with COVID-19, and it is associated with increased risk of in-hospital mortality. The lower platelet count is associated with higher mortality becomes(12). And recent data explained this relationship between thrombocytopenia and progress in CONID-19 through analogy, three mechanisms of thrombocytopenia are direct infection of bone marrow cells by the virus and inhibition of platelet synthesis [10]. Following virus infection, cytokine storm destroys bone marrow progenitor cells and leads to a decrease in platelet production. Lung injury indirectly results in a reduction of platelet synthesis; Platelet destruction by the immune system; Platelet aggregation in the lungs, resulting in micro thrombi and platelet consumption. From other hands; this investigated study

showed that decrees W.B.C. level strongly associated with respiratory symptoms and complication in COVID-19 patients that convenient with other study presented that the US Centers for Disease Control and Prevention (CDC) have released a meta-analysis on the relevance of white blood cell count in severe COVID-19 illness. Experts looked at clinical studies from three databases MEDLINE/PubMed, EMBASE, and CENTRAL(13) that were published between December 1, 2019, and March 28, 2020. At least 1289 COVID-19 cases of varying severity were studied for leukocyte (total white cell count) and lymphocytes (a type of white cell) counts. Leukocytosis (higher than usual white blood cells) and lymphopenia (lower than usual lymphocyte count) were common findings among patients who suffered a severe or critical illness. Among the increased counts, Neutrophils were high however this finding was not consistent. Researchers speculated multiple reasons for a decrease in lymphocyte numbers which may have occurred due to direct infection, inflammation, or inhibition by metabolic disorders. They state that these associations can be crucial in prioritizing patients with severe disease so that treatment therapies can be initiated at the earliest [12-18].

REFERENCES

1. Mizumoto, K. and Chowell G. Estimating Risk for Death from Coronavirus Disease, China,. Emerg Infect Dis. 26(6), p.1.
2. Kumar D, Malviya R SP. Corona virus: a review of COVID-19. Eurasian J Med Oncol. 2020;4:8-25.
3. Bordi L, Nicastri E, Scorzolini L, Di Caro A, Capobianchi MR, Castilletti C LE. Differential diagnosis of illness in patients under investigation for the novel coronavirus (SARS-CoV-2). Eurosurveillance. 27;25(8):2.
4. Velavan TP MC. The COVID-19 epidemic. Trop Med Int Heal. n/a:278–80.
5. Jin YH,Cai L , Cheng ZS,Cheng H,Deng T,Fan YP et al. "A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020;7(1), 4.
6. Christina A. Fennella, Giulia A. Marchetti, Scott S. Davis, Andualem D. Mossie. Prevalence and predictors oral human papillomavirus among HIV-positive women. American Journal of BioMedicine Volume 3, Issue 11, pages 712-724
7. Rt CRNA, Rt-pcr PCR, Rt S, Rt O, Pcr R, Pcr RT, et al. RT-PCR : Two-Step Protocol Two-step Protocol.
8. Al-Tawfiq, J.A. and Memish, Z.A. Diagnosis of SARS-CoV-2 infection based on CT scan vs RT-PCR: reflecting on experience from MERS-CoV. J Hosp Infect. 2020;105(2), pp.
9. Brian S. Singer; Stefan K Blinov. The epidemiological characteristics of Ebola Virus Disease. American Journal of BioMedicine Volume 2, Issue 10, pages 1095-1109 October 2014.
10. Jin, Y. H., Cai, L., Cheng, Z. S., Cheng, H., Deng, T., Fan, Y. P., ... & Han Y. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 7(1), 4.
11. Sarhan AR, Flaih MH, Hussein TA HK. Novel coronavirus (COVID-19) Outbreak in Iraq: The First Wave and Future Scenario. medRxiv.
12. https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020.
13. Yousif NG, Majid Al-Matwari. Overexpression of Notch-1 induced tamoxifen resistance through down regulation of ESR1 in positive estrogen receptor breast cancer. Journal of clinical oncology 2012;e11046-e11046.
14. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 13:1-6.
15. Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S, Long D YL. Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. Platelets. (;31(4):490-6.).
16. Xu P, Zhou Q XJ. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol. 15:1-4.
17. Yousif NG, Ahmed LA, Sadeq AM. The Prevalence of Anemia and Hemoglobinpathies among Students: Cross Section Study. Prensa Med Argent 2020; 106:6.
18. Shah B Navarro, Bintenna M Peiris. Human papilloma virus (HPV) vaccine: Gardasil reactions. American Journal of BioMedicine2014; 2(2):146–155.