

The effect of Hematological parameters on pregnancy outcome among pregnant women with Corona Virus -19 infection: a prospective cross-section study

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Abstract

Coronavirus Disease 2019 (COVID-19), emerged in early December 2019 in China and became a pandemic situation worldwide by its rapid spread to more than 200 countries or territories. The prevalence and evolution of COVID-19 in pregnancy, including the risk of miscarriage in the first and second trimester and early preterm birth. So we need to identify the laboratory parameters capable of discriminating between severe and non-severe cases, or those at high or low risk of abortion, the present study aims to highlight the role of hematological markers (ferritin, D-dimer, CR Protein, ESR, LDH, Random Blood Sugar, hemoglobin, white blood cell & albumin) each one has a role in the development of signs and symptoms. Blood samples were collected from 47 newly diagnosed pregnant women with COVID19 in Najaf-Iraq from June 13 to October 06, 2020. Then the cases followed up for 200 days (two trimesters) about 13 pregnant women aborted before reach to the second trimester, the ANOVA and Kaplan-mier test shows a significantly high level of (ferritin, D-dimmer, CRP, ESR, RBS, and LDH) correlated with abortion and increased rate of loss baby and vice-versa occurs among 34 pregnant women who successfully passed to second trimester, ($P < 0.005, 0.014, 0.003, 0.005, 0.005 \& 0.001$ respectively), Meanwhile the elevated levels of hemoglobin and albumin correlated with a high chance of saving pregnancy period ($P < 0.002, 0.001$ respectively). also, the result shows there is no significant effect of lymphocyte concentration during the pregnancy period in pregnant women with COVID19. From these findings, we can conclude that the changes of hematological parameters correlates with the saving or losing the baby during pregnancy and may help in control the severity of COVID19 infection by using these markers as the prognostic marker

KEYWORDS: *Coronavirus, COVID-19, pregnancy, SARS-CoV-2, severe acute respiratory syndrome coronavirus*

1. INTRODUCTION

COVID-19 is a respiratory illness caused by a new coronavirus SARS-Cov-2 also known as COVID-19. It was first described in December 2019 in Wuhan, China, and has since spread globally [1,6]. Since recording Iraq's first COVID-19 case was reported on 24 February 2020, the COVID-19 pandemic has become very alarming in Iraq, with the country currently reporting new cases every day [2]. It was noted in some study that the largest number of those who were infected between the ages of (31y-40y) [3].

During pregnancy, the implications of COVID-19 infection remain unclear at this moment. Pregnancy is considered high risk as this population remains vulnerable to coronavirus infection. The information about the effect of COVID19 on the pregnancy period, their manifestations, and outcomes remain limited. Most pregnancies had good outcomes, and transmission of SARS-CoV-2 to the infant was uncommon [3].

The study conducted in American Centers for disease control (CDC) suggests that hospitalization rates and ICU admissions in pregnant women diagnosed with COVID-19 are higher than in the non-pregnant population while mortality rates are similar [4]. Another study explains the role of COVID19 in coagulation disorders that may negatively affect pregnancies [5,6].

We need to know if they're negative effects or non on the health of mothers and the fetus so the present study aims to highlight first and second-trimester miscarriage in pregnant women with COVID19 infection.

2. Material & Methods

A prospective cross-section study conducted in Al-Najaf/Iraq in the period between June 13 until October 06, 2020, the study included 70 pregnant women in their first trimester with symptoms like fever, flu-like illness, joint pain, cough, and diarrhea nasopharyngeal swab was taken for all women, 47 of them proved to be positive for COVID-19 by PCR, Group A: 34 Group A pregnant women in the first trimester with COVID-19 reach successfully to second trimester while Group B pregnant women in the first trimester with COVID-19 who aborted. All cases are diagnosed by a physician according to WHO criteria to diagnosed COVID19. All cases with pastmedical diseases or recurrent abortion are excluded from the study design by history. Blood aspirated from each woman with positive PCR after taking their acceptance to participate in the study sent for ferritin, D-dimer, CR Protein, ESR, LDH, Random Blood Sugar, hemoglobin, white blood cell & albumin. Hematological markers include the serological test like IGG and IGM used to follow up cases.

Statistical analysis:

Data were translated into a computerized database structure. Expert statistical advice was sought. Statistical analyses were computer-assisted using SPSS version 23 (Statistical Package for Social Sciences). Horizontal bars indicate the means. For multiple comparisons, p values will be calculated by a one-way ANOVA.

The Kaplan-Meier method with the log-rank test was used to calculate survival rates and differences in survival curves. A receiver operating characteristic (ROC).

3. Results

The present data show the measured of nine hematological markers among pregnant women infected by COVID19 after following up women for 200 days (two trimesters) about 13 pregnant women aborted before reach to the second trimester and the results of blood test show the level of (ferritin, D-dimmer, CRP, ESR, RBC, and LDH) means significantly higher than means of the same hematological marker in about 34 pregnant women who successfully passed to second trimester, as shown in Table 1 and Figure 1. ($P < 0.005, 0.014, 0.003, 0.005, 0.005 \& 0.001$ respectively)

Meanwhile as appears in table 1 and figure 1 the pregnant women with elevated levels of hemoglobin and albumin had a significantly high chance of saving pregnancy period than other groups with low levels, ($P < 0.002$,

0.001 respectively). in another side the statistical result shows there are no significant effect of lymphocyte concentration during pregnancy period in pregnant women with COVID19

Furthermore the reverse occur with (lymphocyte, hemoglobin & albumin level) when patients come with a high concentration the probability of Surviving increased, the Kaplan Meir shows that patients with high concentration have a high chance to survive in the second trimester when compared with low concentration as shown in, Table 4-12 and Figure 4-11, and according to Log-rank test, the mean survival time was significantly higher among cases with high (lymphocyte, hemoglobin & albumin level) concentration at baseline compared to those with lowest concentration (mean survival increased to 200 days) ($P < 0.005, 0.003, 0.002$ respectively).

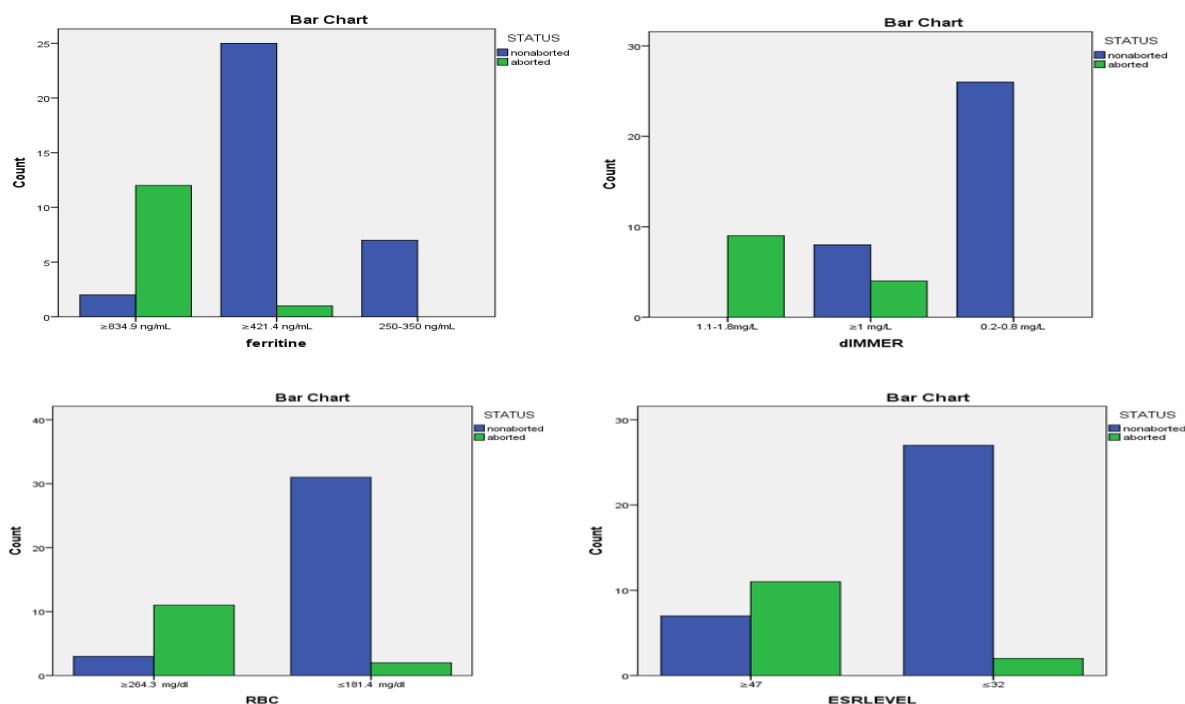
Table (1): The means of a hematological marker according to pregnancy status(aborted/non-aborted) among pregnant women with COVID-19

Variables	Status	No	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		P-value
						Lower Bound	Upper Bound	
ferritin ng/ml	aborted	13	638.13	124.852	32.237	568.99	707.27	0.005
	non aborted	34	267.09	107.957	19.084	228.17	306.02	
	Total	47	385.51	207.758	30.305	324.51	446.51	
D-dimer mg/L	aborted	13	1.3333	.48795	.12599	1.0631	1.6036	0.014
	non aborted	34	.5388	.29846	.05276	.4312	.6464	
	Total	47	.7924	.52215	.07616	.6391	.9457	
CRP mg/dl	aborted	13	19.07	3.127	.808	17.33	20.80	0.003
	non aborted	34	11.06	2.355	.416	10.21	11.91	
	Total	47	13.62	4.576	.667	12.27	14.96	
LDH mg/L	aborted	13	433.00	40.334	10.414	410.66	455.34	0.001
	non aborted	34	260.16	62.519	11.052	237.62	282.70	
	Total	47	315.32	98.802	14.412	286.31	344.33	
Lymphocyte	aborted	13	.4073	.29789	.07692	.2423	.5722	0.081
	non aborted	34	.4739	.29704	.05251	.3818	.5959	
	Total	47	.4628	.29656	.04326	.3757	.5499	
RBS mg/dl	aborted	13	278.60	12.040	3.109	271.93	285.27	0.005
	non aborted	34	113.47	32.822	5.802	101.64	125.30	
	Total	47	166.17	82.608	12.050	141.92	190.42	

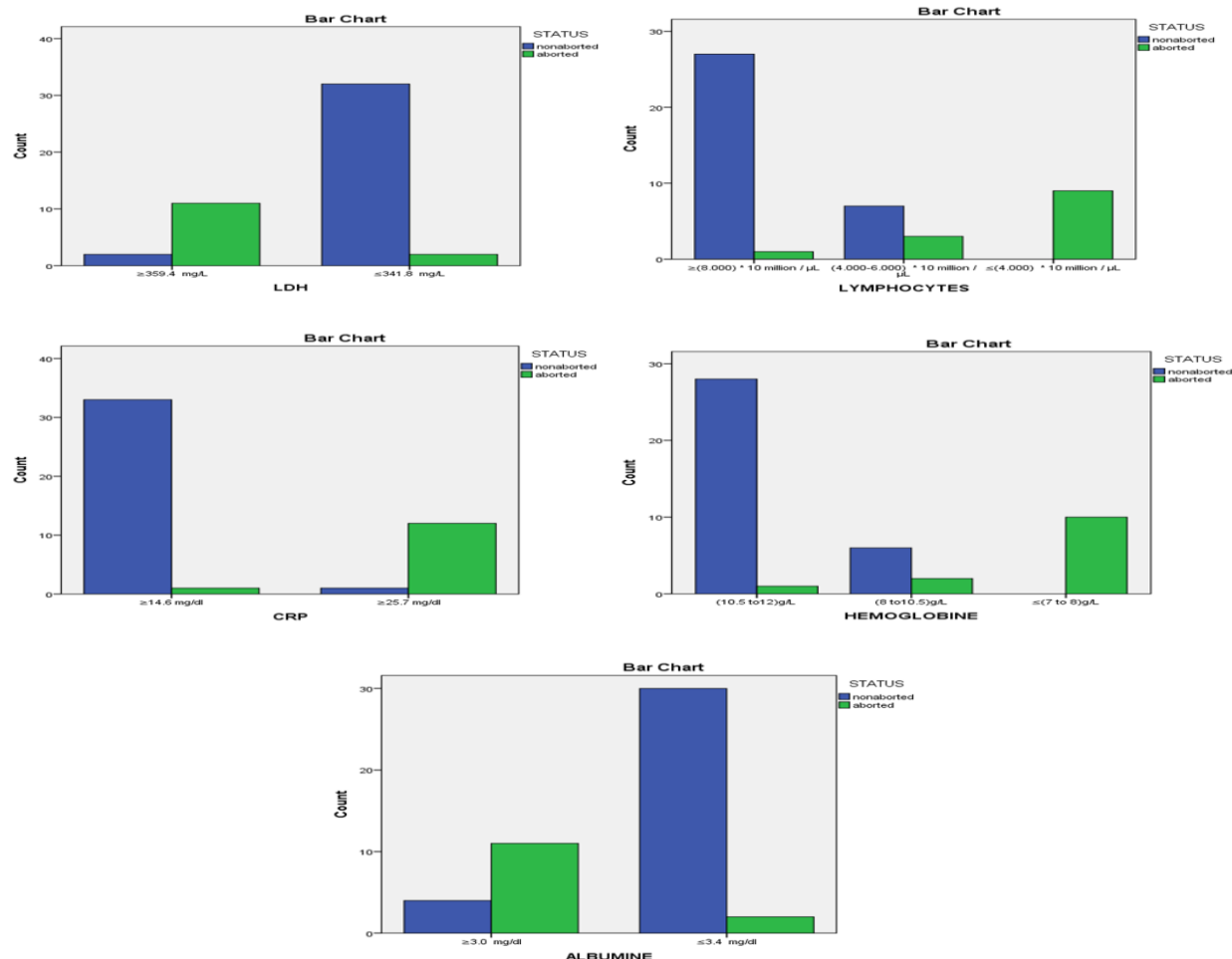
ESR	aborted	13	37.73	4.148	1.071	35.44	40.03	0.005
	non aborted	34	19.53	6.416	1.134	17.22	21.84	
	Total	47	25.34	10.322	1.506	22.31	28.37	
Hemoglobin	aborted	13	2.5385	.66023	.18311	2.1395	2.9374	0.002
	Nonaborted	34	1.2353	.55371	.09496	1.0421	1.4285	
	Total	47	1.5957	.82514	.12036	1.3535	1.8380	
Albumin mg/dl	aborted	13	2.13	.834	.215	1.67	2.60	0.01
	non aborted	34	4.66	1.208	.214	4.22	5.09	
	Total	47	3.85	1.615	.236	3.38	4.33	
IgG	aborted	13	4.53	1.356	.350	3.78	5.28	0.005
	non aborted	34	10.19	1.749	.309	9.56	10.82	
	Total	47	8.38	3.118	.455	7.47	9.30	
IgM	aborted	13	10.20	1.859	.480	9.17	11.23	0.005
	non aborted	34	2.97	2.008	.355	2.24	3.69	
	Total	47	5.28	3.922	.572	4.13	6.43	

N: number, P- Value <0.05; sig: significant, CRP: C-reactive protein, RBC: Red blood cell, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase

Figure(1): Changes in means of a hematological marker according to pregnancy status(aborted/non-aborted)



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The high expression of (ferritin, D-dimmer, CRP, ESR, RBC, and LDH) had a positive correlation with abortion as shown in Table(2), Figure (2). The mean of surviving rate among time decrease with a high concentration of (ferritin, D-dimmer, CRP, ESR, RBC, and

LDH) compared with a mean of low concentration ($P < 0.005, 0.025, 0.005, 0.003, 0.001 \& 0.005$ respectively), this means when these hematological proteins in high concentration the probability of abortion increase and vice versa.

Table (2): Kaplan-Mier Survival Showing the Cumulative Survival and Death Estimates (in Addition to Mean Survival Time) During a Maximum of 2 trimesters (200 days) Follow up Period by COVID19 prognosis and hematological marker categories.

Variables	Mean ^a		95% Confidence Interval		P*
Ferritin con.					0.005
≥834.9 ng/mL	87.600	7.184	73.520	101.680	
≥421.4 ng/mL	134.105	8.601	117.248	150.963	
250-350 ng/mL	132.722	3.185	126.479	138.966	
D-Dimmer con.					0.025
1.1-1.8mg/L	83.423	7.178	69.355	97.491	
>1 mg/L	127.222	7.333	112.850	141.595	

0.2-0.8 mg/L	149.280	3.645	142.136	156.424	
Lymphocytes Con.					0.005
$\geq(8.000) * 10$ million / μL	149.786	3.156	143.599	155.972	
$(4.000-6.000) * 10$ million / μL	108.800	7.182	94.724	122.876	
$\leq(4.000) * 10$ million / μL	74.000	6.416	61.424	86.576	
Overall	130.595	5.400	120.011	141.179	
The hemoglobin levels					0.003
$(10.5 \text{ to } 12)\text{g/L}$	149.897	3.049	143.920	155.874	
$(8 \text{ to } 10.5)\text{g/L}$	106.375	8.967	88.800	123.950	
$\leq(7 \text{ to } 8)\text{g/L}$	76.800	5.840	65.353	88.247	
Overall	130.595	5.400	120.011	141.179	
CRP levels					0.005
$\geq 14.6 \text{ mg/dl}$	150.353	2.608	145.242	155.464	
$\geq 25.7 \text{ mg/dl}$	76.308	5.069	66.372	86.243	
Overall	130.595	5.400	120.011	141.179	
ESR levels					0.003
≥ 47	103.000	9.776	83.839	122.161	
≤ 32	131.907	2.849	126.322	137.491	
Overall	130.595	5.400	120.011	141.179	
The RBC con****.					0.001
$\geq 264.3 \text{ mg/dl}$	82.857	6.489	70.138	95.576	
$\leq 181.4 \text{ mg/dl}$	148.168	3.356	141.590	154.745	
Overall	130.595	5.400	120.011	141.179	
Albumin Con.					0.002
$\geq 3.0 \text{ mg/dl}$	83.767	6.473	71.080	96.454	
$\leq 3.4 \text{ mg/dl}$	148.153	3.363	141.562	154.745	
Overall	130.595	5.400	120.011	141.179	
LDH con.					0.005
$\geq 359.4 \text{ mg/L}$	77.615	5.098	67.624	87.607	
$\leq 341.8 \text{ mg/L}$	148.293	3.273	141.878	154.709	
Overall	130.595	5.400	120.011	141.179	

Table(3): Log Rank (Mantel-Cox) table shows the Test of equality of survival distributions for the different levels of the covid19 prognosis and hematological marker

Log Rank (Mantel-Cox)	Chi-Square	df	P Sig.
Ferritin	11.031	2	.005
D-dimmer	34.327	2	.025
The lymphocyte con.	43.017	2	.003
Hemoglobulin con.	42.622	2	.002
CRP Con.	48.862	1	.005
ESR	17.968	1	.003
RBC	32.095	1	.001

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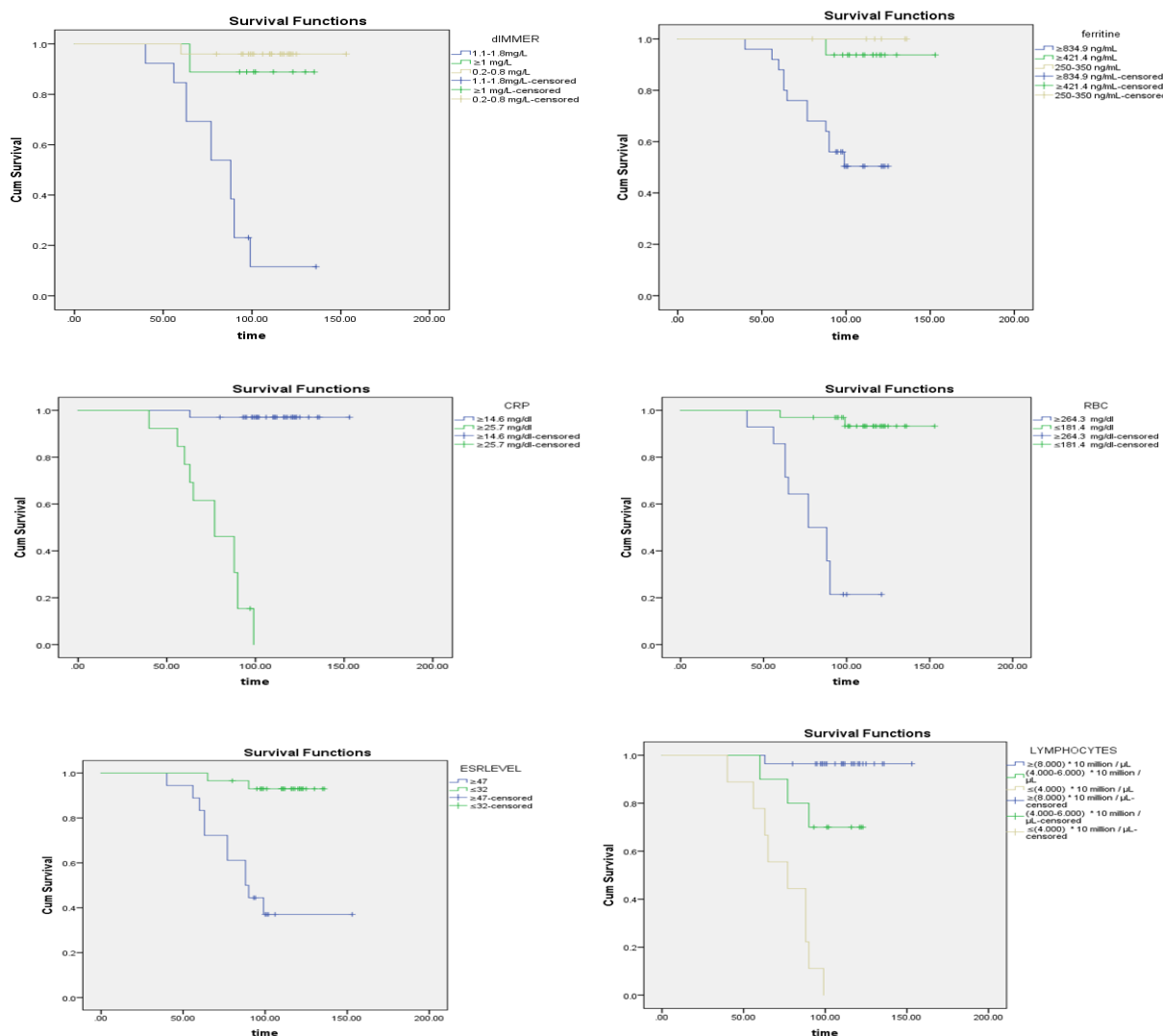
Albumin	28.404	1	.000
LDH	36.124	1	.000

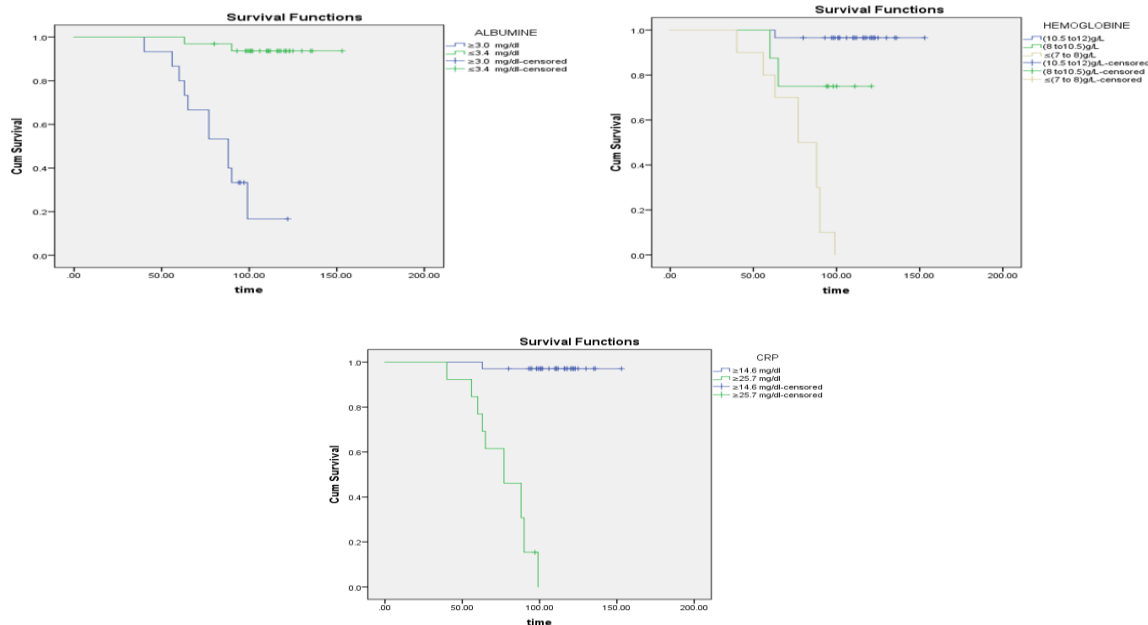
P-Value <0.05;sig:significant. CRP: C-reactive protein, RBC: Red blood cell, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase

All quantitative hematological measurements were tested for their ability to predict a severe disease of COVID 19 patients and risk of abortion. All of them provided a good test in

this context (ROC area ≥ 0.6). the ferritin and RBC were the best among them all, while lymphocyte and albumin considered worthless test as shown in Table (4) and Figures (3)

Figure (3-3): A Survival Curve Comparing the Cumulative Survival Rates During





During a Maximum of 2 trimesters (200 days) Follow up Period by COVID-19 prognosis and hematological marker categories.

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)

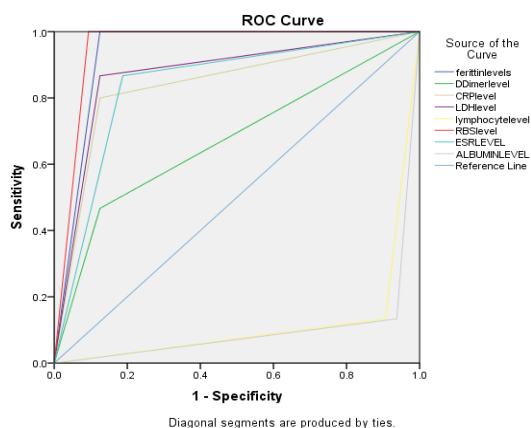


Table (4): The Area Under ROC Curve For hematological marker When Used as a Test to Predict Cases with a risk of abortion in pregnant women with COVID-19

Area Under the Curve		
Test Result Variable(s)	Area	p-value
Ferritin levels	0.938	≤ 0.005
D-Dimer level	0.671	≤ 0.021
CRP level	0.838	≤ 0.005
LDH level	0.871	≤ 0.005
Lymphocyte level	0.114	≤ 0.061
RBS level	0.953	≤ 0.001
ESR level	0.840	≤ 0.001
Albumin level	0.098	≤ 0.071

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 and has now rapidly spread to over 50 countries. For prevention and control of infection, the Taiwan Centers for Disease Control initiated testing for SARS-CoV-2 on January 24th, 2020 for persons suspected of having the disease (7-

11). There is no evidence to suggest that pregnant women are more likely to become seriously ill from COVID-19. However, pregnant women have been included in the list of people at moderate risk (clinically vulnerable) as a precautionary measure. A recent study showed that pregnant women with COVID-19 infection developed mild to moderate symptoms, but blood tests showed abnormalities and elevations in hematological markers that could potentially affect the survival rate of the fetus (13). The statistical results show that 13 pregnant women failed to reach the second trimester, while 43 cases successfully reached it (13). The results also showed that COVID-19 infection outcomes caused elevations in the levels of ferritin, D-dimer, CRP, ESR, RBC, and LDH, which had a negative effect on the health of the pregnancy, while increased levels of hemoglobin and albumin had a highly significant chance of saving the pregnancy period (15,16). Meanwhile, the fetus survival rate decreased with high concentrations of ferritin, D-dimer, CRP, ESR, RBC, and LDH, compared to low concentrations (15,16). This result is in agreement with the findings of Savirón-Cornudella R et al. (15,16). Xu et al. reported retrospective results of five pregnant women at more than 34 weeks' gestation with a positive PCR test for SARS-CoV-2. These women displayed lymphopenia and eosinopenia at the onset of fever, which persisted until they improved after antiviral/antibacterial treatment. In contrast, only one patient had leukopenia, while all the women had anemia, decreased albumin, and increased CRP and D-dimer levels (17). ROC curve analysis showed that ferritin and RBC levels were excellent tests, CRP, LDH, and ESR were very good tests, and D-dimer was a good test to predict women at high risk of abortion. These results are in line with the

findings of Zaigham and Andersson, who showed that laboratory tests for pregnant women who experienced early delivery presented lymphocytopenia (59%) and elevated C-reactive protein (CRP) (70%) (19). The increased levels of CRP and high sensitivity CRP were associated with poor pregnancy outcomes (20).

Many studies have shown that COVID-19 is not fatal for fetuses, unlike other viruses such as Zika and Rubella (17). The possible vertical transmission of the virus was studied by testing for SARS-CoV-2 in amniotic fluid, cord blood, and neonatal pharyngeal swab samples, which were all negative and there were no cases of fetal death (20-22). Additionally, vaginal secretion samples collected from the lower third of the vagina upon admission were also negative (21-22).

Reference

- Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. (2020). "The Continuing 2019-nCoV Epidemic Threat of Novel Coronaviruses to Global Health: The Latest 2019 Novel Coronavirus Outbreak in Wuhan, China." *International Journal of Infectious Diseases*, 91, 264-266.
- "Early COVID-19 Preparation Saved Lives in Iraq." World Health Organization Eastern Mediterranean Regional Office. <http://www.emro.who.int/irq/iraq-news/early-covid-19-preparation-saved-lives-in-iraq.html>.
- Nasser Ghaly Yousif, Ahmed N. Altimimi, Fadhil G. Al-Amran, J. Adrienne Lee, Samar Muayad Al-Fadhel, Salwa Riyadh Hussien, Najah R. Hadi, Maitham G. Yousif, Mohammad AG. Alfawaz, Kareem G. Mohammed. "Hematological Changes Among Corona Virus-19 Patients: A Longitudinal Study."

- Systematic Reviews in Pharmacy, 2020; 11(5), 862-866.
- Ellington S, Strid P, Tong VT, et al. (2020). "Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status, United States." *Morbidity and Mortality Weekly Report*, 69, 769-775.
- Fei Y, Tang N, Liu H, and Cao W. (2020). "Coagulation Dysfunction: A Hallmark in COVID-19." *Archives of Pathology & Laboratory Medicine*, 144, 1223-1229.
- Levi M, Thachil J, Iba T, and Levy JH. (2020). "Coagulation Abnormalities and Thrombosis in Patients with COVID-19." *Lancet Haematology*, 7(6), e438-e440.
- Singhal T. (2020). "A Review of Coronavirus Disease-2019 (COVID-19)." *Indian Journal of Pediatrics*, 13, 1-6.
- Mizumoto K, and Chowell G. (2020). "Estimating Risk for Death from Coronavirus Disease, China." *Emerging Infectious Diseases*, 26(6), 1.
- Kumar D, Malviya R, and SP. (2020). "Corona Virus: A Review of COVID-19." *Eurasian Journal of Medical Oncology*, 4, 8-25.
- Bordi L, Nicastrì E, Scorzolini L, Di Caro A, Capobianchi MR, Castilletti C, and LE. (2020). "Differential Diagnosis of Illness in Patients Under Investigation for the Novel Coronavirus (SARS-CoV-2)." *Eurosurveillance*, 25(8), 2.
- Velavan TP. (2020). "The COVID-19 Epidemic." *Tropical Medicine and International Health*, n/a, 278-280.
- 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.
- Mayeur A, Binois O, Gallot V, Hesters L, Benoit A, Oppenheimer A, Presse M, Zeghari F, Benguigui J, Grynberg M, Frydman N. First follow-up of art pregnancies in the context of the COVID-19 outbreak. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2020 Oct 1;253:71-5.
- Panahi L, Amiri M, Pouy S. Risks of novel coronavirus disease (COVID-19) in pregnancy; a narrative review. *Archives of academic emergency medicine*. 2020;8(1).
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*. 2020 Apr 30;382(18):1708-20.
- Savirón-Cornudella R, Altamirano-Barcia IE, Chedraui P, Andeyro-García M, Tajada-Duaso MC, Pérez-López FR. Coronavirus disease 2019 (COVID-19) and human pregnancy: a scoping review. *Gynecological and Reproductive Endocrinology and Metabolism*. 2020:70-5.
- Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ*. 2020;368:m606.
- Dhama K, Patel SK, Pathak M, Yatoo MI, Tiwari R, Malik YS, Singh R, Sah R, Rabaan AA, Bonilla-Aldana DK, Rodríguez-Morales AJ. An update on SARS-CoV-2/COVID-19 with particular reference to its clinical pathology, pathogenesis, immunopathology and

mitigation strategies. Travel medicine and infectious disease. 2020 May 30:101755.

Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020 Apr 7.

Sadiq, A. M., Hussein, C. M., Yousif, M., & Mohammed, R. (2020). Correlation Between Highly Sensitive C-Reactive Protein Level in Cases of Preeclampsia with or without Intrauterine-Growth Restriction. Indian Journal of Forensic Medicine & Toxicology, 14(4).

Poon LC, Yang H, Lee JCS, et al. ISUOG Interim Guidance on 2019 novel coronavirus infection during pregnancy and puerperium: information for healthcare professionals. Ultrasound Obstet Gynecol. 2020;55:700-8.

Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 (COVID-19) in pregnant women: A report based on 116 cases. Am J Obstet Gynecol. 2020; S0002-9378(20)30462-2.