Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **February 2022; 8(1):146-157**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1064479

One Year Analysis of Hematological and Inflammatory Parameters to Predict the Severity of COVID-19 Infection in Pregnant Women

Seda Keskin[1(ID)], Deha Denizhan Keskin[1(ID)]

[1]Obstetrics and Gynecology Department, Medical Faculty, Ordu University, Ordu, Turkey

Received:28 January 2022, Accepted: 05 February 2022, Published online: 25 February 2022

Abstract

Objective: The study aims to demonstrate the usability of admission hematological parameters in the prognosis of COVID-19 infection in pregnant population and to introduce the cut-offs values of these parameters for pregnant women.

Methods: The cohort of this retrospective study consisted of 71 COVID-19 PCR positive pregnant women who were hospitalized in Ordu University Medical Faculty Training and Research Hospital between 1 May 2020 and 1 May 2021. The pregnant women were divided into two groups based on the severity of the disease.

Results: White blood cell count, neutrophil count and C-reactive protein (CRP) levels was significantly higher (p=0.000, p=0.000), whereas red blood cell count and lymphocyte count were significantly lower (p=0.002, p=0.002) in severe group. High NLR (neutrophil-to-lymphocyte ratio) (p=0.000), dNLR (derived neutrophil-to-lymphocyte ratio) (p=0.000), MLR (monocyte-to-lymphocyte ratio) (p=0.004), PLR (platelet-to-lymphocyte ratio) (p=0.008), NPR (neutrophil-to-platelet ratio) (p=0.005), NLRNPR (neutrophil-to-lymphocyte ratio/neutrophil-to-platelet ratio) (p=0.008) and SII (Systemic immune inflammation index) (p=0.000) were found in severe group.

Conclusion: This paper revealed that severe COVID-19 disease in pregnant women is mainly associated with hematological parameters. Among these parameters NLR, dNLR and SII have largest AUC in ROC, with cutoff values 5.3, 3.52 and 994.8 respectively. Further investigations regarding the use of hematologic tests as prognostic factor of COVID-19 disease severity in pregnant women are needed to assess the risk of serious disease, to predict the prognosis of COVID-19 and to reduce perinatal and maternal morbidity/mortality.

Key words: COVID-19, complete blood count, c-reactive protein, hematological parameters, pregnancy.

Suggested Citation Keskın S, Keskin D D. One Year Analysis of Hematological and Inflammatory Parameters to Predict the Severity of COVID-19 Infection in Pregnant Women Mid Blac Sea Journal of Health Science, 2022; 8(1):146-157

Address for correspondence/reprints:
Deha Denizhan Keskin

Telephone number: +90 (452) 226 52 28
E-mail: dehadenizhankeskin@gmail.com

INTRODUCTION

At the end of 2019, a novel corona virus named COVID-19 was identified in Wuhan city in Mainland China, which caused severe viral pneumonia and spread rapidly. Within three months, the disease was detected in more than 200 countries around the World and COVID-19 was therefore declared as a global pandemic by the World Health Organization (WHO) on the 11th of March 2020 (1). In Turkey, the first polymerase chain reaction (PCR) test positive COVID-19 case was reported on the same date as the declaration, and positive cases started increasing since March 2020. As of May 1, 2021, the total number of cases reached almost 5 million in Turkey (2).

The nucleic acid amplification tests that also known as PCR tests are commonly used to detect COVID-19 in nasopharyngeal and oropharyngeal secretions. Although these tests have high specificity, false negativity rates can increase up to 40% (3). In addition to PCR, CT and X-ray applications are recommended by official guidelines, many studies have revealed alterations in laboratory findings in COVID-19 patients. More than 30 parameters were studied during the pandemic process and various parameters were found to be associated with COVID-19 prognosis, severity, mortality and response to treatments in non-pregnant adult population. Hematological effects including neutrophilia, lymphopenia and thrombocytopenia; immunological effects and also inflammatory indicators including high CRP levels were examined in general population with COVID-19 (4). However, pregnancy have alterations in cell mediated immunity and cardiopulmonary adaptations; and this condition makes the pregnant vulnerable to infectious diseases (5). Also, lung infection with any infectious pathogens in pregnancy is an important mortality and morbidity factor for pregnant population (6).

Hitherto, most studies have described clinical characteristics of pregnant with COVID-19 infection including symptomatology, pregnancy outcomes, lung CT (computed tomography) findings, mother-infant transmissions, routine laboratory scans (7,8). In a large multinational cohort study, it is shown that pregnant women is related with low rate mortality but 11,1% rate of admission to intensive care unit which may increase diverse maternal and perinatal conditions (9). Therefore, blood count parameters and hematological derived inflammatory markers are feasible, accurate and applicable in all health institutions, to discriminate severe cases which would need further care. The hyper inflammation and endothelial damage appear to be the main pathologic mechanism underlying the worsening conditions with COVID-19 infection. Thereof, investigations were concentrated on infectious and inflammatory blood parameters which could predict the prognosis of the patients. Especially, NLR has been used to predict severity of oncological diseases, cardiovascular mortality and also as a prognostic marker in patients with the acute respiratory syndrome (10,11). Besides NLR, importance of PLR which is accepted as a marker of acute inflammation and tendency to thrombosis, has been described to predict the clinical deterioration of the COVID-19 patients (12). SII is also a ratio studied as a prognostic indicator in the sepsis and in the cancer patients and also the COVID-19 infection (13,14).

In our study, we aimed to demonstrate the usability of admission hematological parameters in the prognosis of COVID-19 infection in pregnant population and to introduce the cut-offs values of these parameters for pregnant women. The blood count is an inexpensive, fast, side-effect-free laboratory test that can be applied in any hospital and there is scarce of investigation related with these blood parameters and the indicators derived from peripheral blood parameters, in pregnant population.

METHODS

This single-center, retrospective, cohort study was conducted between May 1th, 2020, and May 1th, 2021, in Ordu University Training and Research Hospital which is a tertiary hospital in the Middle Black Sea Region of Turkey. The hospital has been designated as a corona virus pandemic hospital by the Ministry of Health, and the only hospital in Ordu Province which accepts pregnant women with COVID-19 infection. The present study protocol was approved by the ethics committee of the Ministry of Health Republic of Turkey with issue number 2020-05-11T19_06_54. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

The study group consisted of 71 COVID-19 PCR test positive pregnant women that were hospitalized. The inclusion criteria in our study were COVID-19 pregnant women who were hospitalized in our hospital. Real-time reverse transcriptase polymerase chain reaction (RRT_PCR) tests were performed with Bio Speedy SARS CoV-2 detection kit (Bioeksen R&D Technologies, Istanbul, Turkey) that provided by the Ministry of Health of Turkey. Non-confirmed PCR negative cases, even if they were symptomatic or with a history of contact, were excluded from the study. Exclusion criteria in our study were pregnant women with comorbidities such as hypertension, diabetes, asthma, and morbid obesity. Medical records of pregnant women who were hospitalized during the study period were analyzed retrospectively. Clinical symptoms and other features (age, gestational week, length of hospital stay) were recorded.

The pregnant women were divided into two groups based on the severity of the disease. Thence, there was a non-severe group (consisting of 49 patients) and a severe group (consisting of 22 patients). Severe disease group which requiring oxygen therapy was characterized by dyspnea, shortness of breath, high respiratory rate (>30 breaths per minute), low oxygen saturation (<93% on room air and rest). The other pregnant women, who have been hospitalized and never required oxygen therapy or showed aforementioned symptoms, were described as non-severe group.

The initial triage protocol of inpatient COVID-19 patients includes blood sampling. A blood sample for complete blood count (CBC) was taken from all patients upon admission before any treatment began. CBCs were analyzed within 30 minutes by an automatic blood count device (Sysmex Corporation, ZN 1000i, Kobe, Japan). Simultaneously with CBC other blood sample was taken for measurement of C-reactive protein (CRP) levels by using a spectrophotometric chemical analysis device (Roche Diagnostics, Cobas E 501, California, USA). Demographic characteristics and clinical features of patients are represented in Table 1. Hematologic indices, hematologic ratios and CRP levels was

presented in Table 2. These hematological indices were calculated as NLR, which is the ratio between the count of neutrophils (×109cells/L) and the count of lymphocytes (×109 cells/L), dNLR is the ratio of neutrophils/(white blood cells- neutrophils), PLR is the ratio between the count of platelets (×1011 cells/L) and the count of lymphocytes (×109 cells/L) and the SII is defined as the counts of neutrophils (×109 cells/L) multiplied by the counts of platelets (×1011 cells/L) and divided by the count of lymphocytes (×109 cells/L), NPR is the ratio between the count of neutrophils (×109 cells/L) and the count of platelets (×1011 cells/L).

Statistical analysis

The study aims to demonstrate the usability of admission hematological parameters in the prognosis of COVID-19 infection in pregnant population and to introduce the cut-offs values of these parameters for pregnant women.

For analyzing the results of the study, IBM SPSS Statistics Package (Version 20 Armonk, NY: IBM Corp.) was used. Analyzes were carried out in a 95% (p=0.05) confidence interval. Descriptive statistical methods and correlation analyzes had been used in the study. Descriptive data derived from the study was presented as mean ± standard deviation or median. The normal distribution of numerical variables was studied with the Kolmogorov-Smirnov and the Shapiro-Wilks tests. The independent samples t-test was used when the numerical variables had a normal distribution, or the Mann-Whitney U test was used when the numerical variables did not have normal distribution.

The analysis of the receiver operating characteristic (ROC) curve was used to discover the optimal cut-off values of the levels of the peripheral blood parameters to predict the severity of patients in the study group. AUC was interpreted as excellent if 0.9-AUC-1, good if 0.8-AUC-0.9, moderate if 0.7-AUC-0.8, poor if 0.6-AUC-0.7, and failed if 0.5-AUC-0.6. Multivariate Cox regression analyses were used to evaluate the independent predictors of severity progression of disease.

RESULTS

Totally, 71 COVID-19 PCR test positive pregnant women in Ordu city were enrolled in this retrospective, cohort research. All of the patients included in the study were followed up and treated by hospitalization. Twenty-two of the patients (31%) were in the severe group that requiring oxygen therapy. Dyspnea, high respiratory rate (>30 breaths per minute) and low oxygen saturation (<93% on room air and rest) was observed in this group of patients. There were no fetal or maternal demise along the study period.

The mean age of the entire study cohort was 31.68+6.26 (19-48). And the mean gestational age of pregnant women was 27.72+9.33 weeks. In addition, the majority of patients were in the third trimester with the ratio of 62%, while the rate of first and second trimester pregnancies was 8.4% and 29.6%, respectively. There was no statistically significant difference between the groups in terms of neither age nor gestational week (p=0.193 and p=0.116). However, a significant difference was observed between the groups in terms of length of hospital stay (p=0.000). The hospitalization period of the patients in the severe group that required oxygen therapy was two times longer than the other group (9.45+2.4 vs. 4.9+2.1).

Thirty (42.25%) patients were asymptomatic. In symptomatic patients, headache (70.7%) was the most common symptom followed by fatigue (63.4%) and fever (56%). Dyspnea and shortness of breath was detected in 22 (53.6%) patients and these patients were in the severe group. Cough (48.7%) and diarrhea (31.7%) were the other symptoms. The demographic characteristics and clinical symptoms of patients were recorded and demonstrated in Table 1.

The data as the percentages above the normal reference range for the entire group was also examined. High CRP, lymphopenia, anemia, neutrophilia was found in 83%, 54.9%, 47.8% and 28.1% of patients, respectively. White blood cell count and neutrophil count was significantly higher, whereas red blood cell count and lymphocyte count were significantly lower in severe group. Besides, C-reactive protein was significantly higher in severe group that required oxygen therapy.

COVID-19 PCR positive pregnant women who required oxygen therapy presented significantly higher baseline values of NLR (neutrophil-to-lymphocyte ratio) (9.38 vs. 4.15, p=0.000), dNLR (derived neutrophil-to-lymphocyte ratio) (5.52 vs. 2.68, p=0.000), MLR (monocyte-to-lymphocyte ratio) (0.664 vs. 0.419, p=0.004), PLR (platelet-to-lymphocyte ratio) (208.9 vs. 153.1, p=0.008), NPR (neutrophil-to-platelet ratio) (0.049 vs. 0.033, p=0.005), NLRNPR (neutrophil-to-lymphocyte ratio/neutrophil-to-platelet ratio) (208.9 vs. 153.2, p=0.008) and SII (Systemic immune inflammation index = neutrophils multiplied by platelets and divided by lymphocytes) (1753.7 vs. 833.2, p=0.000). Hematologic indices, hematologic ratios and CRP levels was presented in Table 2.

ROC analysis evaluating COVID-19 severity revealed that optimal cut-off values for most laboratory parameter and blood count derived ratios were statistically significant. The largest AUC for dNLR was 0.921 with the cut-off value of 3.52 (sensitivity 86% and specificity 83%). The second largest AUC of 0.905 was observed in NLR with a cut-off value of 5.3 (sensitivity 81.8% and specificity 81.6%). The excellent AUC which was determined as 0.9-AUC-1, have been observed in NLR and dNLR; good AUC (0.8-AUC-0.9) have been observed in SII; moderate (0.7-AUC-0.8) have been observed in CRP, WBC, RBC, Hb, Hct, Neu, Lym, MLR, PLR, NPR, NLNPR; and the other AUC for blood count parameters have been determined as poor or failed. The sensitivity and specificity values of all laboratory parameters under the optimal cut-off values that statically significant were presented in Table 3.

Potential risk factors, including CRP, WBC, RBC, Hb, Hct, Neu, Lym, NLR, dNLR, MLR, PLR, NPR, SII, NLNPR were investigated using binary logistic regression analysis. In Table 4. MLR (monocyte lymphocyte ratio) (p=0.008, OR=8.63, confidence interval=1.746-42.681), dNLR (p=0.000, OR=3.794, confidence interval=2.016-7.138), NPR (p=0.014, OR=2.749, confidence interval=506.8-1.491) were seen as with the best predictive values for pregnant who may have worse clinical course.

Table 1: Demographic characteristics and clinical features of patients

	Severe Group (n=22)		Non-severe Group (n=49)		P value
	Mean+SD	*Number (Ratio)*	*Mean+SD*	*Number (Ratio)*	
Demografik features					
Age	30.23+5.9		32.33+6.3		0.193
Gestational week	30.32+6.1		26.55+10.3		0.116
Length of hospital stay	9.45+2.4		4.90+2.1		0.000*
Clinical symptoms **					
Fever		14/22 (63.6%)		9/49 (18.3%)	0.000*
Fatigue		11/22 (50%)		15/49 (30.6%)	0.097
Cough		12/22 (54.5%)		8/49 (16.3%)	0.002*
Headache		14/22 (63.6%)		15/49 (28.5%)	0.348
Diarrhea		4/22 (18.1%)		9/49 (18.3%)	0.632

*Statically significant
** Since the grouping was made according to the dyspnea symptom, it is not included in the table

Table 2. Hematologic indices, hematologic ratios and CRP levels

	Overall	Severe Group	Non-severe Group	P value
C-reactive protein (CRP) (mg/L)	23.12+27.19	43.43+38.24	14.03+12.79	0.000*
- >5	59 (83%)	21 (95.4%)	38 (77.5%)	
White Blood Cell Count (WBC) (K/mL)	8.46+3.48	10.50+4.06	7.54+2.76	0.001*
- >1.2	9 (12.6%)	5 (22.7%)	4 (8.1%)	
Red Blood Cell Count (RBC) (K/mL)	3.96+0.49	3.69+0.41	4.07+0.48	0.002*
- <4	44 (61.9%)	18 (81.8%)	26 (53%)	
Hemoglobin (Hb) (g/dL)	11.10+1.36	10.52+1.13	11.3+1.38	0.015*
- <11	34 (47.8%)	14 (63.6%)	20 (40.8)	
Hematocrit (Hct) (g/dL)	33.78+3.58	31.92+2.61	34.60+3.67	0.003*
- <33	34 (47.8%)	16 (72.7%)	18 (36.7%)	
Platelet (Plt) (K/mL)	198+77	196+70	200+80	0.852
Mean Corpuscular Volume (MCV) (fL)	85.69+6.52	86.80+6.43	85.19+6.56	0.342
Mean corpuscular hemoglobin (MCH) (g/dL)	28.19+2.95	28.63+3.05	27.98+2.91	0.397
Mean corpuscular hemoglobin concantration (MCHC) (g/dL)	32.84+1.39	32.93+1.58	32.79+1.30	0.701
Red Cell Distribution Width (RDW)(%)	44.50+5.88	43.25+3.46	45.05+6.64	0.234
Platelet Distribution Width (PDW) (%)	11.48+2.26	11.29+1.85	11.56+2.42	0.634
Platecrit (PCT) (%)	0.200+0.670	0.199+0.069	0.200+0.065	0.958
Mean Platelet Volume (MPV) (fL)	10.06+1.62	10.18+0.76	10.00+1.88	0.665
Neutrophil (Neu) (K/mL)	6.58+2.98	8.76+3.55	5.59+2.07	0.000*
- >8	20 (28.1%)	15 (68.1%)	5 (10.2%)	
Lymphocyte (Lym) (K/mL)	1.37+0.62	1.03+0.45	1.52+0.62	0.002*
- <1.5	39 (54.9%)	18 (81.8%)	21 (42.8%)	
Monocyte (Mono) (K/mL)	0.57+0.30	0.65+0.41	0.53+0.23	0.109
Eosinophil (Eos) (K/mL)	0.045+0.064	0.039+0.057	0.047+0.066	0.622
Basophil (Baso) (K/mL)	0.016+0.016	0.020+0.025	0.013+0.008	0.139
NLR (neutrophil-to-lymphocyte ratio)	5.78+3.64	9.38+3.88	4.15+2.01	0.000*
dNLR (derived neutrophil-to-lymphocyte ratio)	3.57+2.05	5.52+2.34	2.68+1.09	0.000*
MLR (monocyte-to-lymphocyte ratio)	0.495+0.336	0.664+0.353	0.419+0.302	0.004*
PLR (platelet-to-lymphocyte ratio)	170.4+82	208.9+74	153.1+81	0.008*
NPR (neutrophil-to-platelet ratio)	0.038+0.023	0.049+0.026	0.033+0.020	0.005*
MPVPR (mean platelet volum-to-platelet ratio)	0.062+0.032	0.058+0.020	0.064+0.044	0.597
LYM*PLT (lymphocyteXplatelet)	286.0+203	221.1+177	315.1+209	0.072
RDWPR (red cell distribution width-to-platelet ratio)	0.270+0.142	0.000+0.00	0.102+0.30	0.124
NLRNPR (NLR/NPR)	170.4+82	208.9+74	153.2+81	0.008*
SII (systemic immune inflammation index)	1118.4+747	1753.7+782	833.2+528	0.000*

*Statically significant

Table 3. The sensitivity and specificity values of all laboratory parameters under the optimal cut-off values

	AUC	cutoff	*P*	Confidence interval	Sensitivity %	Specificity %
CRP	0.786	15.15	0.000	0.67-0.903	68	67
WBC	0.746	8.63	0.001	0.610-0.882	72.7	73.5
RBC	0.732	3.88	0.002	0.601-0.863	68.2	69.4
Hb	0.704	10.85	0.006	0.571-0.837	63.6	63.3
Hct	0.731	32.8	0.002	0.609-0.854	68	65
Neu	0.794	6.51	0.000	0.666-0.923	77	75
Lym	0.723	1.185	0.003	0.599-0.846	77	67
NLR	0.905	5.3	0.000	0.836-0.975	81.8	81.6
dNLR	0.921	3.52	0.000	0.856-0.987	86	83
MLR	0.743	0.415	0.001	0.622-0.864	77.3	73.5
PLR	0.734	170.7	0.002	0.611-0.856	77.3	71.4
NPR	0.748	0.0355	0.001	0.627-0.869	72.7	75.5
SII	0.857	994.821	0.000	0.766-0.948	86.4	75.5
NLNPR	0.733	172.5	0.002	0.611-0.856	72.7	71.4

Table 4. The Odds ratio and confidence intervals of all laboratory parameters

	P	OR (Odds ratio)	(CI) Confidence Interval
CRP	0.000	1.066	1.011-1.023
WBC	0.004	1.343	1.100-1.638
RBC	0.002	0.135	0.034-0.538
Hb	0.02	0.605	.396-.925
Hct	0.006	0.778	0.650-0.931
Neu	0.001	1.63	1.238-2.152
Lym	0.004	0.195	0.065-0.586
NLR	0.002	1.853	1.395-2.462
dNLR	0.000	3.794	2.016-7.138
MLR	0.008	8.63	1.746-42.681
PLR	0.01	1.009	1.002-1.015
NPR	0.014	2.749	506.8-1.491
SII	0.000	1.002	1.001-1.003
NLNPR	0.012	1.009	1.002-1.015

DISCUSSION

As the COVID-19 pandemic is gradually increasing, early classification of the pregnant patients at high risk of progression to a severe disease is important both to differentiate the clinically important group and also to consider an aggressive intervention and hospitalization. Considering the limited healthcare capacity, early prediction of COVID-19 disease severity should be considered as the main point in combating the pandemic. Only in this way, regardless of the development level of the countries, intensive care unit occupancy rates can be kept at a reasonable level by predicting serious patients in the early period.

In systematic reviews and meta-analysis, alterations in various laboratory parameters have been investigated and linked to COVID-19 severity. Among the other laboratory findings, the most striking test is undoubtedly the CBC. Because CBC is on the one hand a fairly inexpensive, routine and effective test, and on the other hand it is applicable even in peripheral hospitals. And most of studies have

reported that CBC test is valuable in predicting the prognosis of COVID-19, especially in countries with low socioeconomics with limited healthcare opportunities (15-17). Nevertheless, there is inadequate data about blood parameters of pregnant women having COVID-19 disease.

In meta-analysis, it was reported that, neutrophilia, lymphopenia and hence neutrophil lymphocyte ratio correlates with severe COVID-19 disease in adults (18-20). Also in a multi-center study, it is shown that lymphopenia; reduced lymphocyte to leukocyte ratio and increased neutrophil to lymphocyte ratio is indicating pregnant women with acute respiratory syndrome having COVID-19 disease (21). Lymphopenia is not just specific to COVID-19. It has also been seen in other viral causes of pneumonia, especially mostly investigated in influenza cases (22). In our study, in line with the literature, high neutrophil and low lymphocyte counts were found in severe group pregnant patients who needed oxygen therapy. Neutrophilia upon admission was related with 1.6 times risk of getting severe COVID-19 infection in pregnancy.

Beyond the proven knowledge related with neutrophilia and lymphopenia in COVID-19 patients both adults and pregnant ones in terms of disease severity, the ratios of hematological parameters such NLR, PLR, SII and NPR came into prominence to predict COVID-19 disease severity (21,23). NLR and PLR actually have been used to evaluate extension of inflammatory conditions. NLR, especially, is used to decide severity in oncological patients, as an indicator of endothelial dysfunction and an important indicator of cardiovascular and ARDS mortality. PLR have been used as an indicator in acute inflammation and prothrombotic states and as a reflector of cytokine release in COVID-19 infected patients; because platelets not only play a role in homeostasis, also they act in inflammation and host defense (24-29). Until to date, there is no consensus on optimal cut-off value for NLR nor PLR. Cutoff values of 3.3 to 5.9 have been used to predict severity with COVID-19 infection (30-32); while 7.9 to 11.8 cutoff values were used to predict mortality (33,34). This wide range of cutoff values shows us the variability of NLR according to race, gender and specific diseases and condition. So, it must be clearly stated in specific groups like pregnant women with COVID-19 infection.

In a study taking the value of NLR>5, having a NLR bigger than 5 is suggesting getting severe disease with COVID-19 infection (22). In another study, it is suggested that having NLR cutoff as 3.3 to show disease progression from mild to severe in adult group (25). In pregnant with COVID-19 infection, NLR is found to be significantly higher than normal pregnant population (35), also in a multi-center study comparing ARDS having COVID-19 pregnant ones with non-ARDS COVID-19 infection ones, significantly difference have been found when NLR>7.5 was studied as cut-off between two groups (21). Also, it is determined in our results that NLR with a cut-off value of 5.3 (sensitivity 81.8% and specificity 81.6%) was a valuable marker to predict severe course in pregnant patients. Also, PLR in our results were statistically significantly high in severe group (p=0.008); but its AUC was 0.734 and OR was 1.009. However, dNLR which is commonly used in cancer patients to predict mortality and chemotherapy response (36); also, is studied in critically ill COVID-

19 infected patients to predict mortality and severity (37). There are no optimal values or cutoffs for dNLR in pregnant women with COVID-19 infection. In our study, dNLR was found to be significantly high in severe group (p=0.000) and when looked for ROC curve, dNLR showed high AUC (0.921) with a cutoff value of 3.52; with sensitivity 86% and specificity 83% and OR was 3.7 for dNLR in pregnant women. When SII is investigated in our pregnant population, which is an index showing instable inflammatory response, SII was higher in severe group (p=0.000), and AUC in ROC was significantly high for defining cutoff value. There is no study revealing these all-inflammatory indices in pregnant population, but in studies in adult COVID-19 infection, SII is found to be significant (38).

Neutrophils, the main component of the WBC count, are responsible for the production of pro-inflammatory mediators. According to the current knowledge about inflammation, the overproduction of pro-inflammatory mediators that also named cytokine storm has been associated with critical illness. In addition, studies investigating the pathogenesis of COVID-19 revealed that neutrophils can cause organ damage secondary to direct infiltration or coagulopathy (19,23). In our study, it was noted that pregnant women with high WBC levels on admission had developed severe disease, while normal WBC level was found to be a protective factor.

In a study which is comparing the hematological parameters and perinatal outcomes in pregnant women with COVID-19 disease in terms of adverse perinatal outcomes, MLR was found as a supportive diagnostic marker (35). In our study, also, MLR (p=0.008, OR=8.63, confidence interval=1.746-42.681) is found to be a good predictor for severe course in pregnant COVID-19 infected patients when logistic regression was used.

Pregnant women with COVID-19 infection which were enrolled in this study were in first, second and third trimesters. Despite there was no statistical difference between severe and non-severe COVID-19 infected pregnant women, in terms of gestational week, it would be better to investigate trimester specific severity of the hematological parameters. Another limitation is the retrospective design and unfortunately small sample size.

The strength of our study is, to the best of our knowledge, this is the first study comparing large scale of hematological parameters and their derivations in pregnant population. Being a single center study and evaluation of the patients by the same team overall period are other advantages of the study.

CONCLUSIONS

There is scarce information related with pregnancy COVID-19 infection especially clinical course and hematological parameters, despite 16 months have passed with COVID-19 pandemics. The aim of this study was to investigate which hematological parameters are associated with severe COVID-19 disease in pregnant and openly reveal all inflammatory indices which can be easily obtained with a baseline blood count.

This paper revealed that severe COVID-19 disease in pregnant women is mainly associated with leukocytosis, neutrophilia and increased NLR, dNLR, MLR, PLR, NPR, SII and NLNPR. Among these parameters NLR, dNLR and SII have largest AUC in

ROC, with cutoff values 5.3, 3.52 and 994.8 respectively.

Although these markers have been investigated in general population, there is limited number of studies in the literature that conducted among pregnant population. Further investigations regarding the use of hematologic tests as prognostic factor of COVID-19 disease severity in pregnant women are needed to assess the risk of serious disease, to predict the prognosis of COVID-19 and to reduce perinatal and maternal morbidity / mortality.

Ethics Committee Approval: Clinical Studies Ethics Committee of Ordu University, Faculty of Medicine, Decision number: 2018-234 Date: 15 November 2018

Peer-review: Externally peer-reviewed.

Author Contributions: Concept, Design, Materials, Data Collection and Processing S K, Literature Review, Writing, Critical Review D D K

Conflict of Interest: The authors certify that they have no financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Financial Disclosure: The authors declared that this study hasn't received no financial support.

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. 2020. (cited 2021 May 1). Available from: URL: http:/ www.who.int/emergencies/diseases/novel-coronavirus-2019.
2. Turkey Ministry of Health. Coronavirus data. 2020. (cited 2021 May 1). Available from: URL: http:/ covid19.saglik.gov.tr.
3. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction-Based SARS-CoV-2 Tests by Time Since Exposure. Ann Intern Med. 2020;173:262-7.
4. Moutchia J, Pokharel P, Kerri A, McGaw K, Uchai S, Nji M, et al. Clinical laboratory parameters associated with severe or critical novel coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. PLoS One. 2020;15:e0239802.
5. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis. 2006;12:1638-43.
6. Sun G, Zhang Y, Liao Q, Cheng Y. Blood Test Results of Pregnant COVID-19 Patients: An Updated Case-Control Study. Front Cell Infect Microbiol. 2020;10:560899.
7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.
8. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395:809-15.
9. Saccone G, Sen C, Di Mascio D, Galindo A, Grünebaum A, Yoshimatsu J, et al. Maternal and Perinatal Outcomes of Pregnant Women with SARS-COV 2 infection. Ultrasound Obstet Gynecol. 2021;57:232-41.
10. Martínez-Urbistondo D, Beltrán A, Beloqui O, Huerta A. The neutrophil–lymphocyte ratio as a marker of systemic endothelial dysfunction in asymptomatic subjects. Nefrología (Madrid). 2016;36:397-403.

11. Shah N, Parikh V, Patel N, Patel N, Badheka A, Deshmukh A, et al. Neutrophil lymphocyte ratio significantly improves the Framingham risk score in prediction of coronary heart disease mortality: insights from the National Health and Nutrition Examination Survey-III. Int J Cardiol. 2014;171:390-7.

12. Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020;92:1533-41.

13. Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest. 2020;130:2202-5.

14. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20:6212-22.

15. Bao J, Li C, Zhang K, Kang H, Chen W, Gu B. Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. Clin Chim Acta. 2020;509:180-94.

16. Ghahramani S, Tabrizi R, Lankarani KB, Kashani SMA, Rezaei S, Zeidi N, et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: a systematic review and meta-analysis. Eur J Med Res. 2020;25:30.

17. Soraya GV, Ulhaq ZS. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An updated meta-analysis. Med Clin (Barc). 2020;155:143-51.

18. Simadibrata DM, Calvin J, Wijaya AD, Ibrahim NAA. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: A meta-analysis. Am J Emerg Med. 2021;42:60-9.

19. Henry B, Cheruiyot I, Vikse J, Mutua V, Kipkorir V, Benoit J, et al. Lymphopenia and neutrophilia at admission predicts severity and mortality in patients with COVID-19: a meta-analysis. Acta Biomed. 2020;91:e2020008.

20. Li X, Liu C, Mao Z, Xiao M, Wang L, Qi S, et al. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. Crit Care. 2020;24:647.

21. Kazemi Aski S, Norooznezhad AH, Shamshirsaz AA, Mostafaei S, Aleyasin A, Nabavian SM, et al. Clinical features and risk factors associated with acute respiratory distress syndrome in pregnant women diagnosed with COVID-19: a multi-center case-control study. J Matern Fetal Neonatal Med. 2021;8:1-5.

22. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020;18:206.

23. Bg S, Gosavi S, Ananda Rao A, Shastry S, Raj SC, Sharma A, el at. Neutrophil-to-Lymphocyte, Lymphocyte-to-Monocyte, and Platelet-to-Lymphocyte Ratios: Prognostic Significance in COVID-19. Cureus. 2021;13:e12622.

24. Zeng F, Li L, Zeng J, Deng Y, Huang H, Chen B, et al. Can we predict the severity of coronavirus disease 2019 with a routine blood test? Pol Arch Intern Med. 2020;130:400-6.

25. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504.

26. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med. 2020;180:1081-9.

27. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81:e6-e12..

28. Yang M, Ng MH, Li CK. Thrombocytopenia in patients with severe acute respiratory syndrome (review). Hematology (Amsterdam, Netherlands). 2005;10:101-5.

29. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect. 2020;80:656-65.

30. Sun S, Cai X, Wang H, He G, Lin Y, Lu B, et al. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clin Chim Acta. 2020;507:174-80.

31. Song C-Y, Xu J, He J-Q, Lu Y-Q. COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients. MedRxiv. 2020;3:1-22.

32. Ma Y, Shi N, Fan Y, Wang J, Zhao C, Li G, et al. Predictive value of the neutrophil-to-lymphocyte ratio (NLR) for diagnosis and worse clinical course of the COVID-19: findings from ten provinces in China. Lancet. 2020;1-43.

33. Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study. J Med Virol. 2020;92:2573-81.

34. Guo T-M, Tong Y, Chen J, Huang L, Cheng B, Zhou J, et al. Clinical Features Predicting Mortality Risk in Older Patients with COVID-19. Lancet. 2020;1-26.

35. Erol Koç EM, Fındık RB, Akkaya H, Karadağ I, Tokalıoğlu EÖ, Tekin ÖM. Comparison of hematological parameters and perinatal outcomes between COVID-19 pregnancies and healthy pregnancy cohort. J Perinat Med. 2020;49:141-7.

36. Rebuzzi SE, Signori A, Banna GL, Maruzzo M, De Giorgi U, Pedrazzoli P, et al. Inflammatory indices and clinical factors in metastatic renal cell carcinoma patients treated with nivolumab: the development of a novel prognostic score (Meet-URO 15 study). Ther Adv Med Oncol. 2021;13:17588359211019642.

37. Noor A, Akhtar F, Tashfeen S, Anwar N, Saleem B, Khan SA, et al. Neutrophil-to-Lymphocyte Ratio, derived Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio and Lymphocyte-to-Monocyte Ratio as risk factors in critically ill COVID-19 patients, a single centered study. J Ayub Med Coll Abbottabad. 2020;32:595-601.

38. López-Escobar A, Madurga R, Castellano JM, Ruiz de Aguiar S, Velázquez S, Bucar M, et al. Hemogram as marker of in-hospital mortality in COVID-19. J Investig Med. 2021;69:962-9.