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LETTER TO THE EDITOR

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Changes of leukocytes, neutrophils, and lymphocytes count and dependent variables in pregnant women with coronavirus disease 2019 before and after cesarean delivery

Dear Editor,

Coronavirus disease 2019 (COVID-19) has become an emergency which has caused an emergent situation.[1] A recent cross-sectional study has shown a prevalence of 15.4% ($n = 33/215$) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (via reverse transcription polymerase chain reaction [RT-PCR]) among pregnant women who delivered their babies in NewYork which is a notable prevalence.[2]

One of the most important characteristic features of COVID-19 is changes in the leukocytes count in cell blood count accompanied by differentials (CBC Diff). A multi-center study on 1099 patients showed a prevalence of 83.2% for lymphopenia in patients diagnosed with COVID-19.[3] Recent studies evaluated the association of some variables in CBC Diff with severe disease course and/or poor outcomes.[4,5] As an example, acute respiratory syndrome distress (ARDS) among inpatients was significantly associated with decreased lymphocytes and increased neutrophils counts.[4]

Significant changes in leukocytes count following uncomplicated cesarean section with normal postpartum period has been shown as a physiological changes.[6] There is no data of postdelivery changes in CBC Diff values in pregnant patients with COVID-19. Thus, these changes might help us to improve our knowledge regarding the pathophysiology of COVID-19 during pregnancy.

Our objective was to evaluate changes in CBC Diff variables of uncomplicated pregnant women with confirmed COVID-19 infection in two states before and after cesarean delivery (CD).

This retrospective multicentre study was performed between March 3 and May 10, 2020, in five hospitals (two Level III maternity and three general Level II hospitals). COVID-19 infection in pregnant women was defined as at least one of two following criteria: (1) Confirmative RT-PCR for SARS-CoV-2 infection and (2) symptomatic patients with a confirmative chest computed tomography scan in favor of COVID-19. We have included pregnant women diagnosed with COVID-19 attended in our hospitals for delivery of their neonate but only those who have undergone CD. Moreover, pregnant women with no symptoms (explained by Guan et al.[3]) but a confirmative RT-PCR result for COVID-19 who had been referred to our center from other hospitals were included. Exclusion criteria were: (1) Any underlying diseases, (2) pregnancy or surgical or COVID-19 related issues as described by Zhou et al.,[7] and (3) cases undergone intrapartum CD (CD before the beginning of early phases of natural vaginal delivery; due to the significant difference between intrapartum and antepartum CD WBC count).[6] A level III maternity hospital in Tehran for the collection of our control group (October 7–28, 2019) was chosen. The controls were healthy uncomplicated CDs. Lymphopenia was defined as less than 10^3 lymphocytes/mm^3, neutrophils to leukocytes ratio as neutrophils ratio, lymphocytes to leukocytes ratio as lymphocytes ratio, neutrophils to lymphocytes ratio as NLR, and subtraction of NLR mean after and before CD as ΔNLR. To evaluate differences between the groups, independent-samples *t* test, and Mann–Whitney *U* test were used for variables with and without normal distribution respectively. For pre and post-CD evaluation in each group paired-samples *t* test and Wilcoxon signed-rank test were used for variables with and without normal distribution respectively. Any *p*-value less than .05 considered to be statistically significant. All the data analyses were performed by SPSS Version 20 (SPSS Inc.) and all participants have signed a consent form.

This study was approved by the Medical Ethics Committee of Tehran University of Medical Sciences (IR. TUMS. VCR. REC.1398.1082).

Considering inclusion and exclusion criteria, twenty uncomplicated pregnant women with COVID-19 enrolled in this study which 75% ($n = 15/20$) were symptomatic. Also, 38 pregnant women were included as the control group. Gestational age at delivery was significantly lower in the heterogeneous ($p < .05$) and symptomatic COVID-19 group ($p < .01$), however, no statistical difference was found for the age.

Analysis of pre-CD CBC Diff depended variables showed significant decrease in lymphocytes ratio ($p < .01$) and absolute lymphocytes count ($p < .01$) as well as increased NLR ($p < .05$) accompanied with a higher ratio of absolute lymphopenia ($p < .01$) in the heterogeneous group compared to the controls. Moreover, changes in the same variables in each group before and after the CD were investigated. These pre- and post-CD analyzes for variables of heterogenous COVID-19 group showed statistically significant increase in some variables such as leukocytes count ($p < .01$), neutrophils ratio ($p < .01$), and neutrophils absolute count ($p < .05$). On the other hand, pre- and post-CD analyzes for variables of the control group showed statistically significant increase in the leukocytes count ($p < .001$), neutrophils ratio ($p < .01$), absolute neutrophils count ($p < .01$), prevalence absolute lymphopenia ($p < .05$), and NLR ($p < .001$) as well as a decrease in lymphocytes ratio ($p < .01$). Also, according to the results, a significant ΔNLR equal to 1.4 and 3.7 for heterogeneous COVID-19 and control groups (respectively) was calculated which showed a significant difference ($p = .036$). Other variables with significant changes have been shown in the Table 1.

TABLE 1 Demographic, symptoms and laboratory results of heterogeneous COVID-19 and control groups

	Variable	COVID-19 group ($n = 20$)	Control group ($n = 38$)	p Value
Demobiographic and maternal data	Age (years)	31.4 ± 5.8 (30.8–34.3)	32.6 ± 5.4 (30.8–34.3)	.436
	Gestational age at delivery (weeks)	36.8 ± 2.1 (35.8–37.8)	38.0 ± 1.0 (37.6–38.3)	**.036**
Symptoms and history (for patients with COVID-19 infection)	Symptomatic women	15 (75%)	NA	-
	Fever	9 (45.0%)	NA	-
	Dyspnea	12 (60.0%)	NA	-
	Cough	5 (25.0%)	NA	-
	Sore throat	1 (5.0%)	NA	-
	Myalgia	7 (35.0%)	NA	-
	Chest pain	0	NA	-
	Nausea and/or vomiting	0	NA	-
	Living with patients with COVID-19	3 (15%)	NA	-
	Contact with COVID-19 positive cases	5 (25%)	NA	-
Laboratory investigations	Confirmative RT-PCR for SARS-CoV-2	15 (75%)	NA	-
	Pre-CD leukocytes × 10^3/mm^3	9.6 ± 3.8 (7.7–11.4)	10.0 ± 2.2 (9.3–10.7)	.640
	Post-CD leukocytes × 10^3/mm^3	**12.0 ± 4.9 (9.7–14.3)****	**13.7 ± 2.7 (12.8–14.6)*****	.172
	Pre-CD neutrophils ratio (%)	77.3 ± 6.2 (74.4–80.2)	70.6 ± 7.7 (68.0–73.1)	**.001**
	Post-CD neutrophils ratio (%)	**82.9 ± 5.1 (80.4–85.3)****	**80.2 ± 9.6 (77.1–83.4)****	.263
	Pre-CD neutrophils × 10^3/mm^3	7.5 ± 3.3 (5.9–9.1)	7.1 ± 2.1 (6.4–7.8)	.655
	Post-CD neutrophils × 10^3/mm^3	**10.1 ± 4.5 (8.0–12.2)***	**11.0 ± 2.7 (10.1–11.9)****	.411
	Pre-CD lymphocytes × 10^3/mm^3	1.6 ± 0.7 (1.2–1.9)	2.2 ± 0.6 (2.0–2.4)	**.004**
	Post-CD lymphocytes × 10^3/mm^3	1.6 ± 0.6 (1.3–1.9)	1.8 ± 1.0 (1.49–2.19)	.443
	Pre-CD lymphocytes ratio (%)	17.7 ± 5.6 (15.1–20.3)	22.5 ± 6.1 (20.5–24.5)	**.005**
	Post-CD lymphocytes ratio (%)	14.6 ± 5.1 (12.2–17.0)	**13.6 ± 8.1 (10.9–16.2)****	.169
	Pre-CD lymphocytes < 10^3/mm^3 (%)	5 (25%)	0	**.003**
	Post-CD lymphocytes < 10^3/mm^3 (%)	3 (15%)	**4 (12.5%)***	.683
	Pre-CD neutrophils to lymphocytes ratio (NLR)	5.0 ± 2.3 (3.9–6.1)	3.6 ± 2.2 (2.8–4.3)	**.027**
	Post-CD NLR	6.4 ± 2.5 (5.2–7.6)	**7.3 ± 3.3 (6.2–8.4)*****	.334
	(Post-CD NLR) – (Pre-CD NLR) = ΔNLR	1.4 ± 3.6	3.7 ± 3.9	**.036**
	Pre-CD platelets × 10^3/mm^3	212 ± 82 (173–250)	191 ± 47 (176–207)	.306
	Post-CD platelets × 10^3/mm^3	242 ± 119 (186–299)	193 ± 71 (169–216)	.172
	Pre-CD hemoglobin gr/dL	12.5 ± 1.0 (12.0–13.0)	12.3 ± 1.2 (11.9–12.7)	.674
	Post-CD hemoglobin gr/dL	**11.5 ± 1.4 (10.8–12.2)**	**11.4 ± 1.4 (10.9–11.9)*****	.847
	Pre-CD hematocrit (%)	36.4 ± 3.2 (34.9-37.9)	36.2 ± 2.9 (35.2–37.1)	.766
	Post-CD hematocrit (%)	**34.1 ± 3.8 (32.3–35.9)**	**34.2 ± 3.6 (33.0–35.5)*****	.888
Treatments for COVID-19	Antiviral	17 (85.0%)	NA	-
	Antibiotics	20 (100%)	NA	-
	Hydroxychloroquine/chloroquine	18 (90.0%)	NA	-

Note: Bolded and underlined variables had significant changes post-CD compared with their presurgery value. Quantitative results have been shown as mean ± *SD* (95% confidence interval for mean).

Abbreviations: CD, cesarean delivery; COVID-19, coronavirus disease 2019; NA, not applicable.

$^{*}p < .05$.

$^{**}p < .01$.

$^{***}p < .001$.

Moreover, a sub-group analysis for symptomatic COVID-19 confirmed cases (75%, 15/20) was performed. The most common symptoms in the symptomatic group were dyspnea (80%), fever (60%), and myalgia (46.5%), respectively. Analysis of pre-CD CBC Diff depended variables showed significant decrease in absolute lymphocytes count ($p < .01$) and lymphocytes ratio ($p < .05$) as well as increased neutrophils ratio ($p < .01$) and NLR ($p < .05$) in the symptomatic group compared to the controls. Also, analyzes showed statistically significant increase in pre- and post-CD means of leukocytes count ($p < .05$), neutrophil ratio ($p < .05$), and absolute neutrophils count ($p < .05$) in the symptomatic patients. Moreover, ΔNLR for the symptomatic group was calculated as 0.8 which was significantly lower than controls ($p < .05$). Other variables have been shown in the supplementary table.

As, same as the controls, both COVID-19 groups had a significant increase in leukocytes count, neutrophils ratio, and absolute

neutrophils count but not as significant as the control group. Before CD, results have shown significantly lower amounts of lymphocytes count and ratio in COVID-19 groups compared to the controls, however, after CD, none of these variables were significantly different in any of COVID-19 groups compared to the controls. Of the most important findings among the controls were significant changes in the lymphocytes ratio (decrease) and prevalence of lymphopenia (increase) following CD which none of them were observed in any of the COVID-19 groups. These data might be helpful to find the possible hypothesis behind this significant increase in ΔNLR (compare to COVID-19 groups) which might be due to (1) a significant increase of neutrophils (both absolute count and ratio) and (2) a significant decrease in lymphocytes ratio compared to the COVID-19 groups.

A retrospective study of 201 confirmed patients with COVID-19 showed that neutrophilia was associated with increased risk for the development of ARDS.[8] Regarding the other CBC Diff related factors, a systematic review and meta-analysis evaluated a total number of 828 patients with COVID-19 has stated that NLR was significantly increased in patients with more severity of the disease.[5] There are several other studies which have been reviewed by Terpos et al., and they have shown that decreased lymphocytes (count and/or ratio), increased neutrophils (count and/or ratio), and increased NLR are associated with poor outcomes such as development of ARDS or intensive care unit (ICU) admission. Furthermore, the association of lymphocytes ratio with severe disease and fatal outcomes has been performed not just about their admission value, also their value during hospitalization when compared with survived patients.[4]

Altogether, a nonsignificant increase in NLR just after CD in pregnant patients diagnosed with COVID-19 should not concern the clinicians if it is not notable. On the other hand, in case of notable increase in the ΔNLR and/or decrease in lymphocytes absolute count, it is better to be ready for any of the possible mentioned outcomes, such as ARDS. These variables in low resources counties could be a life-saving prediction tool for better care of patients and ICU bed reservations, however, they never grant a certain possibility of prediction.

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