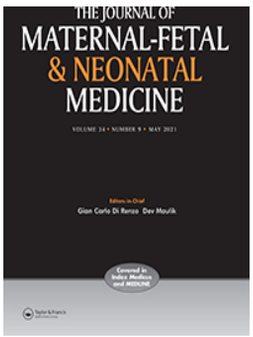

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SHORT REPORT

Clinical features and risk factors associated with acute respiratory distress syndrome in pregnant women diagnosed with COVID-19: a multi-center case-control study

Soudabeh Kazemi Aski[a], Amir Hossein Norooznezhad[b], Amir A. Shamshirsaz[c], Shayan Mostafaei[d,e], Ashraf Aleyasin[f], Seyedeh Maedeh Nabavian[g], Shohreh Alimohammadi[g], Roghaye Ahangari[h], Shideh Ariana[i], Fahimeh Ghotbizadeh[j], Fatemeh Tara[k], Parichehr Pooransari[l], Mahboobeh Gharib Laki[h], Elaheh Zarean[a], Zahra Soleimani[m], Alireza Saliminia[n], Arash Havaei[j], Razieh Akbari[o], Masoud Ramezani[p], Azam Soleimani[q], Mahsa Naemi[f], Alireza A. Shamshirsaz[r] and Sedigheh Hantoushzadeh[a]

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ABSTRACT

Objectives: The aim of this study was to evaluate differences in clinical features and laboratory parameters in critically ill pregnant women with acute respiratory distress syndrome (ARDS) compared to moderate and severe pregnant women with coronavirus disease-2019 (COVID-19) but without ARDS.

Methods: This was a retrospective multicenter study of all pregnant women with COVID-19 diagnosed with ARDS between February 15, and May 1, 2020 in nine level III maternity centers in Iran (ARDS group). The control COVID-19 pregnant women were selected from 3 of 9 level III maternity centers between March 15 and April 20, 2020. Univariate statistics were used to look at differences between groups. Cluster dendrograms were used to look at the correlations between clinical and laboratory findings in the groups. A value of $p < .05$ was considered statistically significant.

Results: Fifteen COVID-19 infected women with ARDS were compared to 29 COVID-19 positive and ARDS negative control (moderate: ($n = 26$) 89.7% and severe: ($n = 3$)10.3%). The mean maternal age (35.6 vs. 29.4 years; $p = .002$) and diagnosis of chronic hypertension (20.0% vs. 0%, $p = .034$) were significantly higher in the ARDS group. There was no significant difference between the two groups in their presenting symptoms. The ARDS group had a significantly higher prevalence of tachypnea (66.6% vs. 10.3%, $p = .042$) and blood oxygen saturation (SpO_2) <93% (66.6% vs. 10.3%, $p = .004$) at presentation. Relative lymphopenia (lymphocyte ratio < 10.5%, 66.6% vs. 17.2%, $p = .002$), lymphocytes to leukocytes ratio (11.3% vs. 17.7%, $p = .010$), and neutrophils to lymphocytes ratio (NLR) >7.5 were significantly different between the two groups (all $p < .05$).

Conclusion: Our data demonstrate that symptom-based strategies for identifying the critically ill pregnant women with SARS-CoV-2 are insufficient; however, vital signs and laboratory data might be helpful to predict ARDS in critically ill COVID-19 pregnant patients.

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Pregnancy; COVID-19; SARS-CoV-2; acute respiratory distress syndrome; lymphocyte; neutrophil; leukocyte

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Due to the urgent and developing nature of the topic, this paper was accepted after an expedited peer review process. For more information about the process, please refer to the Instructions for Authors.

Introduction

In late December 2019, the outbreak of the novel coronavirus (SARS-CoV-2) started in China [1]. The viral disease and infection were named Coronavirus disease 2019 (COVID-19), leading to a global pandemic [2]. Few studies have described presenting symptoms and outcomes of hospitalized pregnant women diagnosed with COVID-19 and predictive characteristics of severely ill pregnant women. Recently, our team reported the first case series of maternal mortality due to COVID-19. According to our knowledge, there is no data yet in the literature for the prediction of critically ill COVID-19 pregnant women [3]. Data compared COVID-19 with previous similar coronavirus diseases (MERS and SARS) has suggested a higher prevalence of ICU admissions as well as adverse fetomaternal outcomes [4].

We aimed to investigate primary clinical features and laboratory findings between critically ill with acute respiratory distress syndrome (ARDS) pregnant women compared to moderate and severe pregnant COVID-19 women without ARDS.

Methods and patients

Methodology

This retrospective multicenter study was performed in nine different level III maternity hospitals (February 15, to May 1, 2020) in Iran and confirmed by Medical Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.VCR.REC.1398.1082). The diagnosis of COVID-19 was based on confirmative reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 infection or chest computed tomography (CT) scan findings [5] in the absence of previous lung disease(s). Subsequently, pregnant women who have been diagnosed with COVID-19 and have developed ARDS during the hospitalization period were included in the study (no exclusion criteria considered).

Concomitantly, during the study, we have selected 3 of 9 hospitals for data collection for a control group which all discharged safely (March 15, to April 20, 2020). The inclusion criteria for the control group was confirmed COVID-19 infection (as mentioned above) in the inpatient pregnant women within two spectrums of moderate to severe categorizes according to the National Institute of Health (NIH) guideline [6]. It should be noted that we have used some data in the ARDS group from our previously descriptive study (except one case) [3].

Data collection

The definition of clinical and laboratory terms has been shown in the supplementary Table 1. All of the demographic and clinical characteristics, presenting clinical features (vital signs and symptoms), laboratory findings (first ran tests), and treatments received were chart abstracted.

Statistical analysis

All data were presented as the mean ± standard deviation for continuous variables. Categorical variables are presented as N (%). The student's t-test (parametric) or the Mann Whitney test (non-parametric) was used to test for statistical significance (two-tailed) between two groups. Two-sided Chi-square/Fisher's exact tests were used to assess the associations between ARDS and non-ARDS groups with the categorical variables. The other statistical analyses including cluster heatmap, multifactor dimensionality reduction (MDR), and area under the curve (AUC) has been stated in the Supplementary File 1. Statistical significance was considered at $p < .05$.

Results

Clinical characteristics

Fifteen pregnant women diagnosed with COVID-19 and ARDS were evaluated as the study group. Among 29 controls, 26 (89.7%) and 3 (10.3%) individuals categorized as moderate and severe COVID-19 infection, respectively. The ARDS group was older compared to the controls (35.6 ± 5.9 vs. 29.4 ± 5.5 years, $p = .002$) (Table 1) and more likely to have chronic hypertension (20.0% vs. 0%, $p = .034$).

Presenting signs and symptoms

In the ARDS group, the three most common symptoms were dyspnea (86.6%), fever (80.0%), and cough (66.6%), respectively. Among the controls, fever (82.7%), cough (65.5%), and dyspnea (58.6%) were the three most prevalent symptoms, respectively. The frequency of each of the symptoms was not significantly different between the two groups (Table 1). Moreover, there was no significant difference in the duration of the symptom(s) for the first visit between two groups ($p = .355$). Comparing vital signs on admission between the groups, the prevalence of tachypnea (66.6% vs. 10.3; $p < .001$) and $SpO_2 < 93\%$ were significantly higher in the ARDS group (66.6% vs. 10.3; $p < .001$, Table 1).

Table 1. Demo/biographic, symptoms, and sings between the studied groups.

	Variable	Critical illness with ARDS (15)	Moderate/sever illness (29)	*p* Value
Demographic data and underlying diseases/situation	Age (years)*	35.6 ± 5.9	29.4 ± 5.5	**.002**
	Gestational age at admission (weeks)*	30.8 ± 6.5	31.7 ± 7.6	.719
	Gravidity*	2.4 ± 1.4	1.9 ± 1.2	.291
	Parity*	1.0 ± 1.3	0.9 ± 1.0	.849
	Twin pregnancy+	2 (13.3%)	2 (6.8%)	.596
	Pre-gestational or gestational diabetes +	2 (13.3%)	1 (3.4%)	.264
	Hypertension+	3 (20.0%)	0	**.034**
	Hypothyroid+	2 (13.3%)	3 (10.3%)	>.999
	Minor thalassemia+	2 (13.3%)	0	.111
	Heart disease+	1 (6.6%)	0	.341
	Asthma	0	2 (6.8%)	.540
	IVF pregnancy+	3 (20.0%)	2 (6.8%)	.319
Symptoms and history	Fever+	12 (80.0%)	24 (82.7%)	>.999
	Dyspnea+	13 (86.6%)	17 (58.6%)	.089
	Cough+	10 (66.6%)	19 (65.5%)	>.999
	Sore throat+	3 (20.0%)	6 (20.6%)	>.999
	Myalgia+	4 (26.6%)	10 (34.4%)	.738
	Hemoptysis+	1 (6.6%)	1 (3.4%)	>.999
	Chest pain+	1 (6.6%)	1 (3.4%)	>.999
	Nausea and/or Vomiting+	1 (6.6%)	3 (10.3%)	>.999
	Diarrhea+	0	0	–
	Duration of symptom(s) to first visit (days)*	4.4 ± 4.6	3.3 ± 2.7	.355
	Contact with COVID-19 confirmed case(s)+	4 (26.6%)	2 (6.8%)	.159
Signs	Body temperature ≥ 37.8 °C+	11 (73.3%)	13 (44.8%)	.111
	Body temperature ≥ 38.0 °C+	9 (60.0%)	11 (37.9%)	.210
	Body temperature °C*	38.1 ± 0.9	37.7 ± 0.6	.114
	Heart rate ≥ 100 beats per minute+	12 (80.0%)	17 (58.6%)	.195
	Heart rate (beats per minute)*	117.1 ± 21.5	105.7 ± 18.7	.078
	Systolic blood pressure < 85 mmHg+	0	0	–
	Systolic blood pressure (mmHg)*	123 ± 23	111 ± 10	.091
	Respiratory rates ≥ 24 breaths per minute +	10 (66.6%)	3 (10.3%)	<**.001**
	Respiratory rates (breaths per minute)*	26.6 ± 6.4	19.4 ± 2.9	**.001**
	O_2 saturation in room < 93%+	10 (66.6%)	3 (10.3%)	<**.001**
	O_2 saturation in room (%)*	89.4 ± 5.9	95.1 ± 3.2	<**.001**

ARDS: acute respiratory distress syndrome; IVF: *in vitro* fertilization; + indicated as *n*/*N* (%).
*indicated as mean ± SD.
Bold values suggest statistically significant variables.

Laboratory results

Significantly higher counts of leukocytes ($p = .03$) and absolute neutrophils counts ($p = .016$) as well as decrease hemoglobin ($p = .006$) were found in the critically ill group compared to the other group. There were significant differences in clinically relevant ratios in the ARDS versus non-ARDS group; specifically, relative lymphopenia ($p = .002$), neutrophils to leukocytes ratio (NLR) or neutrophils ratio ($p = .004$), lymphocytes to leukocytes ratio or lymphocytes ratio ($p = .010$), and neutrophils to lymphocytes ratio >7.5 or NLR >7.5 ($p = .001$) significantly differed between two groups. Creatinine (Cr), blood urea nitrogen (BUN), and alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) were significantly higher in ARDS group ($p = .002$, $p = .020$, $p = .002$, $p = .005$ and $p = .027$, respectively, Table 2). The results of cluster heatmap, MDR, and AUC regarding the evaluated variables are given in Supplementary File 1.

Discussion

The results from the clinical characteristics, vital signs, and presenting symptoms demonstrated that older maternal age, underlying chronic hypertension, increased respiratory rate, and decreased SpO_2 were significantly different between the two groups.

Table 2. Laboratory results and differences between the studied groups.

	Variable	Critical illness with ARDS (15)	Moderate/sever illness (29)	*p* Value
COVID-19 test	SARS-CoV-2 confirmative RT-PCR^{+}	12 (80.0%)	26 (89.6%)	.394
Complete blood count (CBC) with differentials and ratios	Leukocytes $\times 10^3$/mm3*	12.0 ± 4.7	9.1 ± 3.7	**.030**
	Lymphopenia (cells $< 1 \times 10^9$/mL)*	5 (33.3%)	7 (24.1%)	.722
	Relative Lymphopenia (lymphocytes $\leq$ 10.5%)$^{+}$	10 (66.6%)	5 (17.2%)	**.002**
	Lymphocytes ($\times 10^9$/mL)*	1.3 ± 0.6	1.4 ± 0.5	.750
	Neutrophils ($\times 10^9$/mL)*	10.3 ± 4.1	7.3 ± 3.5	**.016**
	Neutrophils to leukocytes to ratio (%)*	85.6 ± 4.9	77.7 ± 9.3	**.004**
	Lymphocytes to leukocytes ratio (%)*	11.3 ± 5.2	17.7 ± 8.4	**.010**
	Neutrophils to lymphocytes ratio*	9.0 ± 3.8	6.2 ± 5.8	.099
	Neutrophils to lymphocytes ratio > 7.5 (%)$^{+}$	11 (73.3%)	6 (20.6%)	**.001**
	Platelets $< 146 \times 10^3$/mL^{+}	4 (26.6%)	3 (10.3%)	.207
	Platelets $\times 10^9$/mL	198 ± 81	200 ± 49	.926
	Hemoglobin < 9.5 gr/dL^{+}	2 (13.3%)	0	.111
	Hemoglobin, gr/dL*	10.7 ± 1.6	11.9 ± 1.0	**.006**
C reactive protein (CRP)	Elevated CRP (>8.1 mg/L or + or higher) $^{+}$	13/14 (92.8%)	21/25 (84.0%)	.636
	CRP (mg/L)	73.6 ± 59.2	35.7 ± 22.9	.134
Kidney function tests	Creatinine, mg/dL^{+}	0.8 ± 0.2	0.7 ± 0.1	**.002**
	Blood urea nitrogen, mg/dL	16.2 ± 9.3	9.1 ± 4.5	**.020**
Liver enzymes	Aspartate aminotransferase (U/L)	98.8 ± 124.9	29.8 ± 12.2	**.005**
	Aspartate aminotransferase > 32 U/L	9 (60.0%)	9/24 (37.5%)	.170
	Alanine aminotransferase, (U/L)	56.4 ± 50.0	20.2 ± 11.0	**.002**
	Alanine aminotransferase > 25 U/L	11 (73.3%)	6/24 (25.0%)	**.007**
Lactate dehydrogenase (LDH)	LDH (U/L)	793 ± 509	431 ± 165	**.027**
	LDH > 524 U/L^{+}	8/13 (61.5%)	4/19 (21.0%)	**.030**

ARDS: acute respiratory distress syndrome; RT-PCR: reverse transcriptase polymerase chain reaction; CRP: C-reactive protein.
+indicated as *n*/*N* (%).
*indicated as mean ± SD.
Bold values suggest statistically significant variables.

Moreover, the investigations showed a significant difference in primary laboratory results in each group mostly ratios including lymphocytes and neutrophils as well as LDH, BUN, and Cr.

The mean age for in the ARDS group was greater than 35 years old equal to advanced maternal age (AMA). AMA is associated with both pregnancy morbidities, including hypertensive disease [7] as well as adverse pregnancy outcomes, including stillbirth and miscarriage [8]. Moreover, being older [9] and hypertension (most prevalent comorbidity in COVID-19 patients) [10] have been reported as strong risk factors for patients with COVID-19 for both mortality and morbidities [9,10]. After reporting maternal/neonatal death in pregnant patients diagnosed with COVID-19 in a case series, the importance of certain evaluations in these groups of the population has been highlighted [3].

A similar study by Wu *et al.*, [9] in a non-pregnant population has been conducted on the adults diagnosed with COVID-19 infection (inpatients) in two groups of patients: with and without ARDS. As in our study, they demonstrate that COVID-19 patients with ARDS were older and had a significantly higher admission respiratory rate (>24 breaths/minute). Their study showed that the presenting symptoms were not different between each group, except for dyspnea ($p < .001$). [9] This difference may be related to the pregnancy associated symptom of dyspnea [11] (especially in the third trimester).

The population-based study from the United Kingdom Obstetric Surveillance System was performed on 427 inpatients confirmed COVID-19 pregnant cases. The most prevalent symptoms were fever, cough, and breathlessness which was similar to our study. As they have shown, among patients with confirmed SARS-COV2 test, 9% ($n = 40$) required level III critical care. However, the authors did not state any other similar data in sub-groups to compare them with our results [12].

The strengths of this study include a great number of critically ill COVID-19 pregnancy patients with ARDS requiring level III maternity hospitals. Our study is not without limitations. First, as with any retrospective analysis, the strength of our findings is limited by the prevalence of rare outcomes. Then, we believe further researches with more laboratory parameters such as D-dimer, CRP, interleukin 6, and procalcitonin levels at admission may be helpful. Also, as Di Renzo and Giardina [13] stated, the risk of thromboemboli is as important as ARDS and we suggest further studies consider it as well as ARDS.

Conclusion

It seems symptom-based strategies for identifying critically ill pregnant women with SARS-CoV-2 infection are insufficient as they do not correlate with disease course. Although all pregnant women with suspicion of SARS-CoV-2 infection should be monitored carefully, we suggest that those with advanced maternal age and chronic hypertension are observed more closely for the development of ARDS. It may also be possible to predict ARDS in COVID-19 pregnant patients using reductionist correlations with laboratory and clinical findings. The possibility of ARDS development should not be ever underestimated in pregnant women with moderate COVID-19.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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