

## Severe COVID-19 and Its Related Factors in Pregnant Women: A Multi-Center Cross-Sectional Study

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### Abstract

**Background & Aims:** Pregnant women are at a higher risk of contracting COVID-19 due to their weakened immune systems. There are various related factors for severe COVID-19 in pregnant women. This study aimed to assess the severe COVID-19 rate and its associated factors among Iranian pregnant women.

**Materials & Methods:** In this multi-center cross-sectional study from 21 March 2020-21 March 2021, all pregnant women (N=488) with COVID-19 who were admitted to healthcare centers in three counties (Mahabad, Miandoab, Bukan) in Iran were enrolled. Patients were categorized into two groups; hospitalized (severe COVID-19) and non-hospitalized. Data were collected through medical records using a researcher-made questionnaire. Statistical analysis was performed using multivariate logistic regression.

**Results:** The mean age of pregnant women was 29.8±6.37 years and 19.9% were hospitalized (N=89). The COVID-19 hospitalization in pregnant women was significantly associated with fever (temperature ≥38 C) [aOR = 3.59, (95%CI; 2.08-6.17)], shortness of breath [aOR = 2.12, (95%CI; 1.24-3.61)], diagnosis of COVID-19 in the second trimester [aOR = 4.48, 95%CI; 1.48-13.58], residence in the urban area [aOR = 0.45, (95%CI; 0.24-0.84)], and diploma and more education level [aOR = 0.58, (95%CI; 0.33-0.98)].

**Conclusion:** Urban residency and higher education level were protective factors. Fever, shortness of breath, and diagnosis of COVID-19 in the second trimester of pregnancy were related factors for hospitalization. Early diagnostic and therapeutic interventions for pregnant women with positive COVID-19 tests are essential in disease control. A longitudinal study with appropriate follow-up time to identify factors related to severe COVID-19 among pregnant women is needed.

**Keywords:** Severe, Hospitalization, COVID-19, Pregnancy, Risk factors

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### Introduction

The COVID-19 pandemic spread rapidly in the world and caused the biggest changes in healthcare systems (1) Coronavirus leads to pulmonary infection with flu-like symptoms such as fever (temperature ≥38

C), cough, shortness of breath, fatigue, and headache. Symptoms can range from being asymptomatic to severe acute respiratory syndrome, leading to pneumonia and respiratory failure (2, 3).

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The immune system during pregnancy is affected by signals produced by the placenta (4). Multiple studies have shown that pregnancy is associated with more severe infection and mortality. Adverse consequences are more prominent during pandemics, especially in women who have respiratory system diseases (5, 6). During pregnancy, physiological ventilation increases excessively, leading to 21% increase in oxygen consumption and 9.5-25% decrease in functional residual capacity (6, 7). In addition, changes in the nasal mucosa caused by progesterone facilitate virus retention in the upper respiratory tract. As a result, the removal of the virus by the host becomes more difficult (8).

During the SARS pandemic, a high rate of mortality was reported in pregnant women. In addition, higher rates of morbidity and mortality were observed in this group compared to non-pregnant patients (9). There are also reports of increased pregnancy complications during the MERS pandemic (10). According to these studies, the Centers for Disease Control and Prevention (CDC) has emphasized the special requirements and precautions for pregnant women and considered this group at high risk for COVID-19 infection (11).

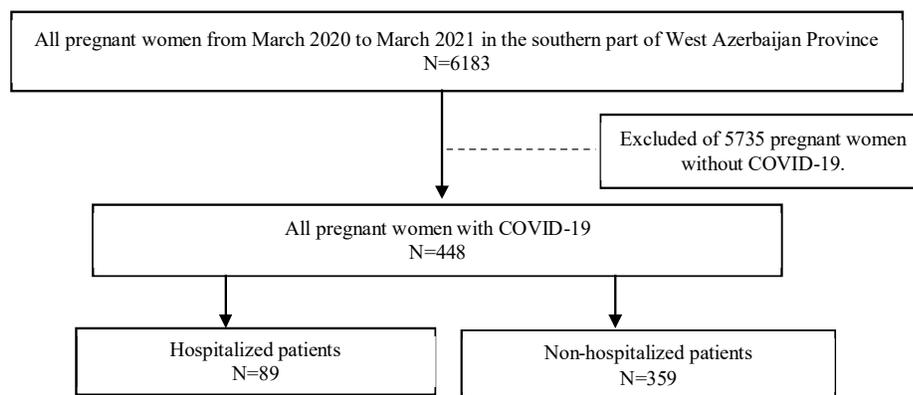
Information about specific risks among pregnant women is necessary to develop evidence-based guidelines for the management of this high-risk group

(12). Even though the related factors for severe COVID-19 among pregnant women have been studied worldwide (13, 14), there is a paucity of literature in Iran. Findings from other international studies may not apply to the Iranian population because of cultural and local practice differences. Therefore, the aim of this study is to determine the related factors of severe COVID-19 in Pregnant Women in Iran.

## Materials & Methods

### Study design, period, and setting:

The current multicenter cross-sectional study was performed from March 21, 2020 to March 21, 2021, including all pregnant women with COVID-19 (N=448) who had presented to healthcare centers in three counties in the southern part of West Azerbaijan Province in Northwest of Iran (Bukan, Mahabad, and Miandoab). In this study, COVID-19 was confirmed in all pregnant women with positive RT-PCR test results at any stage of pregnancy, irrespective of clinical signs and symptoms. Patients' information was extracted from the electronic medical record registered in the National Health System. Participants were classified into two groups: non-hospitalized (N=359) and hospitalized (N=89) (Figure 1). Hospitalized patients were considered to have a severe COVID-19 infection.



**Fig.1.** Flowchart of study participants

**Outcome variable:**

The outcome variable in this study was severe COVID-19, which was determined by the hospitalization of pregnant women with COVID-19 based on the information obtained from electronic health records. Hospitalized pregnant women were those who had a history of hospitalization for at least three days during pregnancy due to COVID-19 infection.

**Inclusion criteria:**

All pregnant women with COVID-19 diagnosed in health and medical centers during the pandemic were included in this study. The diagnosis was confirmed by using a nasopharyngeal RT-PCR swab test for COVID-19. Of note, the diagnosis was made based on the positive RT-PCR test result at any stage during pregnancy, irrespective of clinical signs and symptoms.

**Data collection methods:**

The data of all pregnant women with COVID-19 (non-hospitalized and hospitalized) were extracted from electronic medical records registered in National Health System. The data included sociodemographic characteristics, history of current infection, pregnancy, comorbidities, and care status. A standardized medical record form was used to collect the data. If the information was incomplete, the data was obtained from the health department.

**Data management and statistical analysis:**

Data was first cleaned. Categorical and continuous variables were described as N (%) and mean ± standard deviation (SD), respectively. To investigate the related factors to severe COVID-19, univariable and

multivariable logistic regression analysis were utilized. Variables with p-value < 0.2 in the univariable analysis were entered into a multivariable logistic regression. Assumptions of logistic regression were met. P-values < 0.05 were considered statistically significant.

**Ethical consideration:**

This study was approved by the Research Ethical Review of Urmia University of Medical Sciences (approval number: IR.UMSU.REC.1399.352). The need for Informed Consent was waived by the ethics committee of Urmia University of Medical Sciences due to the retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations.

**Results**

**Demographic and socio-economic characteristics of the study participants:**

Between 21 March 2020 and 21 March 2021, a total number of 488 pregnant patients with COVID-19 diagnosis were included in this study. The characteristics of these patients are summarized in Table 1. The mean age of the participants was 30.4 ± 7.3 years for the hospitalized group and 29.7 ± 6.1 years for the non-hospitalized group. Compared to the hospitalized group, the non-hospitalized patients were more from rural areas (24.7% vs. 13.7%). Moreover, the educational level was under diploma in 68.5% of pregnant women in the hospitalized group and 55.7% of patients in the non-hospitalized group. The majority of the participants were housewives 419 (93.5%).

**Table 1.** Demographic characteristics of study participants

Variables	Non-hospitalization	Hospitalization	Total	P-value
	N (%)	N (%)	N (%)	
<b>Age (mean± SD)</b>	29.74±6.10	30.43±7.38	29.88±6.37	0.365
<b>Residency</b>				
<b>Rural</b>	47 (13.1)	22 (24.7)	69 (15.4)	Ref
<b>Urban</b>	312 (86.9)	67 (75.3)	379 (84.6)	0.007

Education level				
>diploma	200 (55.7)	61 (68.5)	261 (58.3)	Ref
≤ diploma	159 (44.3)	28 (31.5)	187 (41.7)	0.029
Occupation				
Housekeeper	336 (93.6)	83 (93.3)	419 (93.5)	Ref
Employer	23 (6.4)	6 (6.7)	29 (6.5)	0.908

### The incidence of severe COVID-19 disease among Iranian pregnant women:

The incidence of severe COVID-19 disease among Iranian pregnant women was found to be 19.9% (Figure 2).

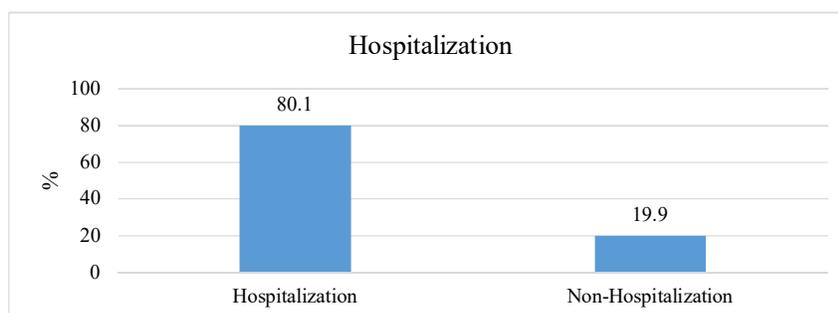


Fig. 2. The incidence of hospitalization among Iranian pregnant women with COVID-19 (N=488).

### Distribution of hospitalizations during trimesters of pregnancy among Iranian pregnant women:

The distribution of hospitalizations during trimesters of pregnancy among Iranian pregnant women with COVID-19 is shown in Figure 3.

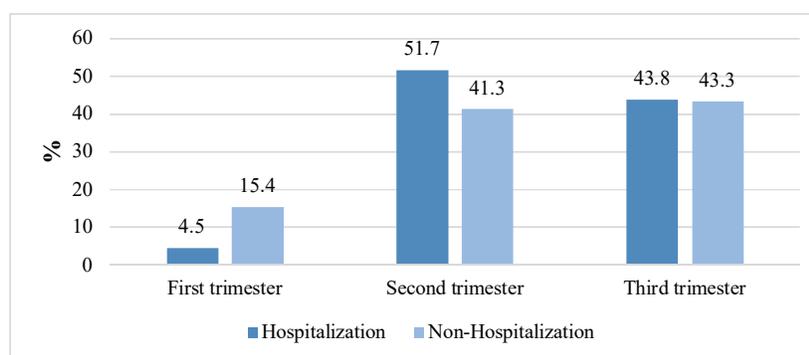


Fig. 3. Distribution of hospitalizations during trimesters of pregnancy among Iranian pregnant women with COVID-19 (N=488)

### Clinical characteristics of study participants:

The mean prepregnancy BMI for the hospitalized group was higher than the non-hospitalized group

( $28.60 \pm 5.03$  vs.  $27.24 \pm 4.71$ ). Patients in the hospitalized group were more likely to have fever (44.9% vs. 16.8%), cough (64.8% vs. 51.8%), and shortness of breath

(52.3% vs. 29.2%). Moreover, more than half of these patients were infected with COVID-19 during the second trimester (51.7%) (Table 2).

**Table 2.** Clinical characteristics of study participants

Variables	Non-hospitalization	Hospitalization	Total	P-value
	N (%)	N (%)	N (%)	
<b>Pre-pregnancy BMI (mean± SD)</b>	27.24±4.71	28.60±5.03	27.51±4.81	0.017
<b>Blood group</b>				
<b>A</b>	142 (39.7)	37 (41.6)	179 (40)	Ref
<b>B</b>	74 (20.7)	16 (18)	90 (20.1)	0.574
<b>AB</b>	25 (7)	5 (5.6)	30 (6.8)	0.613
<b>O</b>	117 (32.6)	31 (34.8)	148 (33.1)	0.951
<b>Fever</b>				
<b>No</b>	298 (83.2)	49 (55.1)	347 (77.6)	Ref
<b>Yes</b>	60 (16.8)	40 (44.9)	100 (22.4)	<0.001
<b>Cough</b>				
<b>No</b>	173 (48.2)	31 (35.2)	204 (45.6)	Ref
<b>Yes</b>	186 (51.8)	57 (64.8)	243 (54.4)	0.032
<b>Shortness of breath</b>				
<b>No</b>	254 (70.8)	42 (47.7)	296 (66.2)	Ref
<b>Yes</b>	105 (29.2)	46 (52.3)	151 (33.8)	<0.001
<b>Gestational age at the time of diagnosis</b>				
<b>First trimester</b>	56 (15.4)	4 (4.5)	59 (13.2)	Ref
<b>Second trimester</b>	148 (41.3)	46 (51.7)	194 (43.4)	0.008
<b>Third trimester</b>	155 (43.3)	39 (43.8)	194 (43.4)	0.051

**Related factors for severe COVID-19:**

Univariate and multivariate analyses of related factors for severe COVID-19 in pregnant women are shown in Table 3. Crude analysis showed that hospitalization was associated with residence in the urban area, above diploma education, pre-pregnancy BMI, fever (temperature  $\geq 38$  C), cough, shortness of breath, and diagnosis of COVID-19 in the second trimester ( $P < 0.05$ ). Adjusted analysis showed that

hospitalization was associated with fever (aOR = 3.59, 95%CI 2.08-6.17,  $P < 0.001$ ), shortness of breath (aOR = 2.12, 95%CI 1.24-3.61,  $P = 0.006$ ) and diagnosis of COVID-19 in the second trimester (aOR = 4.48, 95%CI: 1.48-13.58,  $P = 0.008$ ). Also, residence in urban areas (aOR = 0.045, 95%CI: 0.24-0.84,  $P = 0.013$ ), and higher level of education (above diploma) (aOR = 0.058, 95%CI: 0.33-0.98,  $P = 0.049$ ), were protective factors.

**Table 3.** Crude and adjusted logistic regression analyses of factors associated with severe COVID-19 among Iranian pregnant women with COVID-19 (N=448)

Variable	Hospitalized N (%)	Non-hospitalized N (%)	Crude			Adjusted		
			cOR	95% CI	P-value	aOR	95% CI	P-value
<b>Age (year) (mean± SD)</b>	30.43±7.38	29.74±6.10	1.01	0.98-1.05	0.365	-	-	-
<b>Residency</b>								
<b>Rural</b>	22 (24.7)	47 (13.1)	Ref	Ref	Ref	Ref	Ref	Ref
<b>Urban</b>	67 (75.3)	312 (86.9)	0.46	0.26-0.81	0.007	0.45	0.24-0.84	0.013
<b>Education level</b>								
<b>&lt;diploma</b>	61 (68.5)	200 (55.7)	Ref	Ref	Ref	Ref	Ref	Ref
<b>≥diploma</b>	28 (31.5)	159 (44.3)	0.57	0.35-0.94	0.029	0.58	0.33-0.98	0.049
<b>Occupation</b>								
<b>Housekeeper</b>	83 (93.3)	336 (93.6)	Ref	Ref	Ref	-	-	-
<b>Employer</b>	6 (6.7)	23 (6.4)	1.05	0.42-2.67	0.908	-	-	-
<b>Pre-pregnancy BMI (mean± SD)</b>	(28.60±5.03)	(27.24±4.71)	1.06	1.01-1.11	0.017	1.05	0.99-1.12	0.055
<b>Fever</b>								
<b>No</b>	49 (55.1)	299 (83.2)	Ref	Ref	Ref	Ref	Ref	Ref
<b>Yes</b>	40 (44.9)	60 (16.8)	4.05	2.45-6.69	<0.001	3.59	2.08-6.17	<0.001
<b>Cough</b>								
<b>No</b>	32 (35.2)	173 (48.2)	Ref	Ref	Ref	Ref	Ref	Ref
<b>Yes</b>	57 (64.8)	186 (51.8)	1.71	1.05-2.77	0.032	1.23	0.71-2.12	0.453
<b>Shortness of breath</b>								
<b>No</b>	43 (47.7)	254 (70.8)	Ref	Ref	Ref	Ref	Ref	Ref
<b>Yes</b>	46 (52.3)	105 (29.2)	2.65	1.65-4.26	<0.001	2.12	1.24-3.61	0.006
<b>Gestational age at the time of diagnosis</b>								
<b>First trimester</b>	4 (4.5)	56 (15.4)	Ref	Ref	Ref	Ref	Ref	Ref
<b>Second trimester</b>	46 (51.7)	148 (41.3)	4.27	1.47-12.42	0.008	4.48	1.48-13.58	0.008

Variable	Hospitalized	Non-hospitalized	Crude			Adjusted		
			cOR	95% CI	P-value	aOR	95% CI	P-value
<b>Third trimester</b>	39 (43.8)	155 (43.3)	3.46	1.18-10.12	0.024	3.02	0.99-9.18	0.051
<b>Blood group</b>								
<b>A</b>	37 (41.6)	143 (39.7)	Ref	Ref	Ref	-	-	-
<b>B</b>	16 (18)	74 (20.7)	0.83	0.43-1.6	0.574	-	-	-
<b>AB</b>	5 (5.6)	25 (7)	0.77	0.27-2.14	0.613	-	-	-
<b>O</b>	31 (34.8)	117 (32.6)	1.01	0.59-1.74	0.951	-	-	-

### Discussion

Pregnant women are among the high-risk groups for severe COVID-19 infection (15). Our results showed that the mean age of pregnant women was 29.8±6.37 years and 19.9% were hospitalized. The COVID-19 hospitalization in pregnant women was significantly associated with fever (temperature ≥38 C), shortness of breath, diagnosis of COVID-19 in the second trimester, residence in the urban area, and diploma and more education level.

Our results showed that the educational level and residential area were associated with the severity of COVID-19. The severity of COVID-19 was lower in pregnant women living in urban areas and with a higher level of education compared to pregnant women living in rural areas with a lower level of education. This may be because living in urban areas and having a higher education level can lead to a faster diagnosis so that the necessary interventions can be carried out sooner. The study conducted by Menezes et al. showed that pregnant women who live in peri-urban areas are more at risk for severe COVID-19 than others (16). The results of our study did not show any association between age and the severity of COVID-19. This is not consistent with Allotey et al. and Rezaei et al. studies (17, 18) but is consistent with a study conducted by Barbero et al. (19).

In this study, four fifths of pregnant women with severe COVID-19 had fever. Our results showed that pregnant patients with fever, cough, and shortness of breath were, respectively, 4.05, 1.71, and 2.65 times more likely to have severe COVID-19 compared to pregnant women without these symptoms. This is consistent with most studies showing that the most common symptoms in hospitalized pregnant women with COVID-19 are fever, cough, and shortness of breath (19, 20, 21, 22).

The results of our study showed that with every unit increase in prepregnancy BMI, the odds of developing severe COVID-19 increase by 1.06 times. This is consistent with recent studies (19, 23). We observed that patients with COVID-19 diagnosis during the second trimester of pregnancy are 4.27 times more likely to develop severe COVID-19 compared to women diagnosed with COVID-19 during the first trimester of pregnancy. This is consistent with the study by Sahin et al., which showed that most pregnant patients with severe and critical COVID-19 were diagnosed in the second trimester of pregnancy (24).

In this study, most patients with COVID-19 in both groups had A blood group (40%); however, no association was observed between blood groups and the severity of COVID-19. This is consistent with recent studies (24, 25). Some of the differences in the findings

of this study and previous studies that investigated the related factors of severe COVID-19 in pregnant women could be due to different criteria defining severe COVID-19 infection such as hospitalization or ICU, mechanical ventilation, and death, or due to differences in the distribution of medical pregnancy characteristics, demographic conditions.

One of the strong points of the present study is all confirmed pregnant women with COVID-19 were included in the study for a whole year in three counties. Another strength of this study is its high generalizability because the participants were among the Kurdish, Turkish and Persian populations with a similar culture to those of other parts of Iran and even neighboring countries. The main limitations of this study include that inherited from the cross-sectional study design, it is not possible to make causal inferences from the relationships observed in this study. Another limitation is that RT-PCR test result may be a false positive reported by several pregnant women infected with COVID-19.

### **Conclusion**

In the present study, the incidence of severe COVID-19 disease among Iranian pregnant women was approximately 20%. Residency, education level, pre-pregnancy BMI, fever, cough, shortness of breath, and gestational age at the time of diagnosis were determined to be independent-related factors for hospitalization among pregnant women with COVID-19 in Iran. Knowing the related factors for hospitalization among pregnant women with COVID-19 can help in strategic planning, rapid prevention, diagnosis, and therapeutic interventions. It can also guide future policies in allocating clinical and public health resources. Therefore, we highly suggest that pregnant women should be evaluated for fever, shortness of breath, and cough during the first admission. We also recommend

that undereducated pregnant women with confirmed COVID-19 during the second trimester of pregnancy, who are living in rural areas, should be more carefully monitored and cared for. Conducting a longitudinal study with an appropriate follow-up period to determine the related factors of severe COVID-19 among pregnant women is suggested.

### **Ethical consideration**

The study received was approved by the Ethics Committee of Urmia University of Medical Sciences (NO: IR.UMSU.REC.1399.352).

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### **Declaration of Interests Statement**

The authors declare no conflict of interest.

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### **Data availability**

The datasets during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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