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Exploring factors influencing COVID-19 severity: a matched case-control study

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Abstract. – OBJECTIVE: COVID-19, first identified in December 2019, quickly became a global pandemic and remains a significant public health concern. Robust data is rare, especially in pregnant women. The symptoms of this disease range from mild to severe respiratory distress syndrome and mortality. The present study aimed to evaluate the factors influencing COVID-19 severity in women to be better prepared in case of a new epidemic.

PATIENTS AND METHODS: This retrospective matched case-control study based on body mass index, smoke, and drug use was conducted on all women hospitalized with COVID-19 at Afzalipour Hospital in Kerman, Iran from the beginning of 2020 to 2021. In this study, 130 female patients with COVID-19 were included, with 65 patients in the case group (moderate and severe cases of COVID-19) and 65 patients in the control group (mild cases of COVID-19). The data were entered into the Stata software, and to determine the effective risk factors for the severity of COVID-19 disease, both univariate and multivariable conditional logistic regression analyses were utilized, assuming individual matching. Finally, the odds ratios (OR), along with 95% confidence intervals (CI), were estimated.

RESULTS: The average age of women in the case group was 36.92 ± 7.07 years, compared to 30.12 ± 6.27 years in the control group. Among all patients, 50% were pregnant, with a mean gestational age of 30.03 weeks. Significant factors affecting disease severity included age, education, employment status, place of residence, insurance coverage, comorbidities, and pregnancy status. The highest adjusted odds ratio for severe COVID-19 was associated with comorbidities (OR = 7.8, 95% CI: 2.3-11.1), while the lowest was associated with urban residence (OR = 2.8, 95% CI: 1.02-4.5). Overall, significant predictors of severe COVID-19 included age over 30, urban residence, lack of insurance, a short duration between diagnosis and hospitalization, comorbidities, and non-pregnancy.

CONCLUSIONS: The study identified several significant predictors of severe COVID-19 among women, including age over 30, urban residency, lack of insurance coverage, presence of comorbidities, and non-pregnancy, all of which were associated with a heightened risk of severe illness. Notably, comorbidities emerged as the strongest predictor. These findings underscore the critical need for targeted interventions to protect vulnerable populations.

Key Words:
Clinical features, COVID-19, Pregnant women, Comorbidities, Disease severity.

Introduction

COVID-19 first emerged in Wuhan, China, in December 2019 and rapidly spread globally, leading the World Health Organization to declare it a pandemic on March 11, 2020[1]. Since then, millions have been infected, and many lives have been lost due to the virus[2].

The clinical presentation of COVID-19 ranges from mild respiratory symptoms to severe illness and death, with the elderly and individuals with underlying conditions, such as hypertension, diabetes, respiratory and heart diseas-

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es, and obesity, being at higher risk for severe outcomes[3-5]. Pregnant women are particularly vulnerable to COVID-19 due to physiological changes in their immune and cardiorespiratory systems, which increase their susceptibility to hypoxia and respiratory pathogens. Mechanical and biochemical factors during pregnancy also reduce lung function, raising concerns about the impact of the COVID-19 pandemic on this population[6].

Infections from viruses such as influenza, H1N1, SARS, and COVID-19 have been linked to adverse pregnancy outcomes, including spontaneous abortion, preterm birth, intrauterine growth restriction, increased risk of ectopic pregnancy, intensive care unit (ICU) admissions, venous thromboembolic events, and higher mortality rates[7,8]. It is reported[6] that 6.9% of pregnant women with COVID-19 develop severe disease. Studies[9] have highlighted fever, cough, and shortness of breath as common symptoms, with severe cases leading to ICU admission and death. Additionally, preterm birth, cesarean sections, and potential effects on neonatal Apgar scores remain significant concerns in pregnant women with COVID-19[10,11].

This study aims to assess the factors contributing to the severity of COVID-19 in women, particularly pregnant women. Identifying these factors is essential for improving preparedness and response strategies in future pandemics by enabling healthcare systems to better prevent, diagnose, and treat the disease in this vulnerable population.

Patients and Methods

This study utilized a retrospective matched case-control design. The study population comprised all women hospitalized due to COVID-19 at Shahid Afzalipour Kerman Educational Referral Hospital from March 2020 to the end of March 2021. Based on the research design and available sample size, 65 women were included in the case group (with moderate to severe illness) and 65 women in the control group (with mild illness). Disease severity was defined following Cascella et al[12] protocol as mild or moderate-to-severe. Inclusion criteria required a confirmed COVID-19 diagnosis through reverse transcription-polymerase chain reaction (RT-PCR), regardless of clinical symptoms. Women with active cancer or those who were hospitalized more than once were excluded from the study.

Both case and control groups were matched based on body mass index (BMI, kg/m²), smoking habits, drug use, and alcohol consumption. Data were collected using a structured questionnaire that included variables such as BMI, smoking status, drug use, alcohol consumption, age, marital status, education level, employment status, economic status, place of residence, health insurance coverage, pregnancy status, gestational age (in weeks), time interval between diagnosis and hospitalization, and the presence of comorbidities (such as diabetes, hypertension, chronic respiratory diseases, asthma, kidney diseases, cardiovascular diseases, immunocompromised status, and other conditions).

Additionally, information regarding treatments received (e.g., antibiotics, antivirals, anticoagulants, oxygen therapy), clinical symptoms (fever, shortness of breath, cough, diarrhea), and COVID-19 outcomes (duration of hospitalization, intubation, ICU admission, mortality) was extracted from medical records. If pregnancy-related outcomes were not available in the medical records, patients were contacted to gather information on outcomes such as miscarriage, preterm birth, intrauterine death, and mode of delivery (vaginal or cesarean section). Patient age and diagnostic criteria were obtained from medical records. For pregnant women, BMI was recorded from the first trimester. None of the study participants had received the COVID-19 vaccine.

The primary outcome of this study was to identify the factors influencing the severity of COVID-19 in women. The secondary outcome was to examine the specific COVID-19-related outcomes in pregnant women, including maternal and neonatal complications.

Statistical Analysis

All statistical analyses were conducted using STATA version 17 (College Station, TX, USA). The normality of variable distributions was assessed with the one-sample Kolmogorov-Smirnov test. Qualitative variables were described as frequency (percentage), and comparisons between groups were made using Chi-square or Fisher's exact tests, as appropriate. Quantitative variables were presented as mean ± standard deviation (SD) and compared between groups using the Student's *t*-test. Both univariate and multivariate conditional logistic regression analyses were performed, account-

ing for individual matching. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated. It is important to note that the data were initially matched for BMI, smoking, and substance use. Statistical significance was determined when the *p*-value was lower than 0.05.

Results

The average age of women in the case group was 36.92 ± 7.07 years, compared to 30.12 ± 6.27 years in the control group. Additionally, the mean BMI in the case group was 25.23 ± 4.11, while in the control group, it was 26.33 ± 5.37. Smoking and substance use were reported by 3.06% (2 out of 65) and 6.15% (3 out of 65) of women in both groups, respectively. None of the participants reported alcohol consumption. Among all the patients, 50% (65 out of 130) were pregnant, with a mean gestational age of 30.03 weeks (ranging from 8 to 40 weeks).

To identify significant factors influencing disease severity, conditional logistic regression analysis was performed, with a significance level set at $p = 0.1$, to ensure important variables were not overlooked. The results showed that age, education level, employment status, place of residence, insurance coverage, comorbidities, and pregnancy status were significant predictors of COVID-19 severity. The highest odds ratio (OR) for severe COVID-19 was associated with patients hospitalized within 24 hours of diagnosis (OR = 6.1, 95% CI: 1.06-13.4), while the lowest OR was linked to those receiving antiviral treatment (OR = 0.2, 95% CI: 0.03-0.6). A summary of factors affecting COVID-19 severity can be found in Table I.

After identifying variables that significantly influenced the severity of COVID-19 ($p < 0.1$) through univariate conditional logistic regression analyses, these variables were simultaneously entered into a multivariable conditional logistic regression model to account for potential confounders. A stepwise approach was employed for confounder elimination and adjustment of factors, allowing for the extraction of the most significant variables (Table II). Key factors influencing the severity of the disease included age over 30, urban residence, lack of insurance, hospitalization within 24 hours of diagnosis, comorbidity, and non-pregnancy. The highest odds ratio for severe COVID-19 was observed with comorbidity (OR = 7.8). After adjusting for other variables, the odds ratio for severe COVID-19 in non-pregnant women was 3.4 (95% CI: 1.69-7.83) (Table II).

As shown in Table III, the length of hospital stay was significantly longer in the case group compared to the control group (9.28 ± 6.84 days *vs*. 4.77 ± 4.27 days). Intubation was required in 24.6% of patients (16 out of 65) in the severe group. While there were no mortalities in the mild group, the mortality rate in the severe group was 12.31% (8 out of 65 patients), with three of the fatalities occurring in pregnant women. A detailed comparison of the clinical features and outcomes of COVID-19 between the case and control groups is presented in Table III.

As shown in Table IV, 6.4% of pregnant women with COVID-19 experienced miscarriage. Additionally, 18.46% had preterm labor, and 15.46% underwent cesarean section. Maternal complications of COVID-19 in pregnant women are summarized in Table IV.

Discussion

The emergence of COVID-19 in 2019 has created a global health crisis, posing significant challenges for healthcare systems in preventing and treating the disease[13], especially for vulnerable subgroups such as women[14]. This study aimed to assess the factors contributing to the severity of COVID-19, specifically in women. Based on the results of univariate conditional logistic regression, women aged 30 years or older, with university education, residing in urban areas, without health insurance, non-pregnant, and hospitalized within less than 24 hours of diagnosis, as well as those with comorbidities, exhibited higher odds ratios for severe COVID-19 compared to their counterparts. Conversely, women receiving antiviral treatment had a lower odds ratio for severe COVID-19 compared to those receiving oxygen therapy. Multivariate conditional logistic regression further identified age over 30 years, urban residence, lack of insurance, hospitalization within 24 hours of diagnosis, comorbidity, and non-pregnancy as significant risk factors associated with severe COVID-19. Notably, comorbidity had the highest odds ratio for severe COVID-19 (OR = 7.8), followed by lack of insurance (OR = 4.9). After adjusting for other variables, the odds ratio for severe COVID-19 in non-pregnant women was 3.6 (95% CI: 1.69-7.83), indicating a strong association with disease severity. These findings

Table I. Factors affecting the severity of COVID-19 disease using the conditional logistic regression model.

Variable	Case group (n = 65)	Control group (n = 65)	Odds ratio (95% CI)	*p*-value
Age (years)				
< 30	36 (55.4%)	11 (17%)	1	0.03
≥ 30	29 (44.6%)	54 (83%)	1.3 (1.1-2.8)	
BMI (kg/m²)				
< 18.5	2 (3.07%)	2 (3.07%)	-	-
18.5-24.9	36 (55.4%)	36 (55.4%)		
25-29.9	20 (30.8%)	20 (30.8%)		
> 30	7 (10.8%)	7 (10.8%)		
Education level				
Illiterate/Primary	50 (76.9%)	32 (49.2%)	1	
Secondary/Diploma	10 (15.4%)	27 (41.5%)	0.9 (0.8-8.7)	0.1
University	5 (7.7%)	6 (9.3%)	2.6 (2.8-4.9)	0.02
Marital status				
Single	16 (24.6%)	21 (32.3%)	1	
Married	49 (75.38%)	44 (67.7%)	1.03 (0.4-12.3)	0.4
Employment status				
Housewife	53 (81.5%)	49 (75.4%)	1	
Employed	12 (18.5%)	16 (24.6%)	1.8 (2.9-4.8)	0.01
Economic status				
Low	8 (12.3%)	14 (21.5%)	1	
Medium	38 (58.7%)	31 (47.7%)	0.05 (0.7-4.7)	0.2
High	19 (30%)	20 (30.8%)	0.9 (0.8-3.2)	0.9
Residence				
Rural	18 (27.7%)	29 (44.6%)	1	
Urban	47 (72.3%)	36 (55.4%)	3.9 (2.1-6.7)	0.001
Health insurance				
Yes	48 (73.8%)	60 (92.3%)	1	
No	17 (26.2%)	5 (7.7%)	3.3 (1.3-6.8)	0.02
Pregnant				
Yes	25 (38.5%)	48 (73.8%)	1	0.001
No	40 (61.5%)	17 (26.2%)	4.7 (3.7-17.8)	
Time from diagnosis to admission (hours)				
< 24	24 (36.9%)	57 (87.69%)	1	
≥ 24	41 (63.1%)	8 (12.3%)	6.1 (1.06-13.4)	0.001
Comorbidity				
No	39 (60%)	44 (67.7%)	1	
Yes	26 (40%)	21 (32.3%)	4.5 (1.9-11.8)	< 0.001
Type of treatment received				
Oxygen therapy	21 (32.3%)	58 (89.2%)	1	
Antibiotics	51 (79.0%)	61 (93.8%)	0.7 (0.1-3.2)	0.1
Antivirals	25 (38.5%)	41 (63.1%)	0.2 (0.03-0.6)	0.001
Anticoagulants	60 (92.3%)	64 (98.5%)	1.2 (0.4-1.9)	0.2

underscore the importance of considering multiple factors simultaneously when assessing the risk of severe COVID-19 and offer valuable insights for risk stratification and targeted interventions.

Booth et al[15] significantly contributed to understanding factors influencing susceptibility to severe illness and mortality from COVID-19 by incorporating various readily available indica-

Table II. Risk factors associated with the severity of COVID-19 using multiple logistic regression model.

Risk factors	Adjusted odds ratio	95% CI	*p*-value
Age over 30 years	3.5	1.1-6.5	0.002
Urban residence	2.8	1.02-4.5	0.001
Lack of insurance	4.9	3.2-8.9	0.003
Less than 24 hours between diagnosis and hospitalization	5.3	13.4-1.9	0.004
Comorbidity	7.8	2.3-11.1	0.0001
Non-pregnancy	3.6	1.69-7.83	0.001

tors such as patient attributes, comorbidity profiles, and real-time symptom monitoring. Their meta-analysis[15], which specifically investigates the impact of pre-existing conditions like hypertension, diabetes, and chronic kidney disease (CKD) on COVID-19 outcomes, revealed a trend towards increased risk with diabetes (OR: 1.99, 95% CI: 0.92-4.29). However, hypertension and CKD did not show a significant elevation in risk. This nuanced understanding is crucial for developing effective diagnostic and prognostic models, as well as informing clinical management strategies for high-risk patients[16]. Additionally, McConnell et al[17] found that severe COVID-19 in adults was associated with public or no insurance, with individuals lacking private health insurance having a 1.9-fold higher risk of COVID-19-associated hospitalization compared to those with private insurance.

In our study, most pregnant women had mild COVID-19, consistent with the findings by Ayed et al[18], who reported mild symptoms in most pregnant women with positive COVID-19 tests. Breslin et al[19] also demonstrated that 86% of pregnant women with COVID-19 experienced mild severity. The most common symptoms in our study were cough, shortness of breath, and fever, which aligns with findings by Ellington[20], who noted cough as the most prevalent symptom in pregnant women with COVID-19.

Our study found that 15.46% of pregnant women with COVID-19 underwent cesarean sections, and three pregnant women (6.4%) died. Additionally, 46.18% of pregnant women experienced preterm birth, with a higher rate of 56.1% observed in other studies[21]. Fayazi et al's[22] review identified preterm birth as a common neonatal complication of COVID-19 and noted that most deliveries were cesarean sections. Preterm birth in pregnant women with COVID-19 may be attributed to factors such as fetal distress due to maternal fever, inflammatory conditions, respiratory distress, or treatment-related complications. Emergen-

Table III. Comparison of clinical characteristics between the case and control groups[a].

Risk factors	Adjusted odds ratio	95% CI	*p*-value
Underlying diseases			
Heart disease	3 (4.6%)	4 (6.2%)	0.33*
Asthma	3 (4.6%)	7 (10.8%)	0.43*
Diabetes	15 (23.1%)	5 (7.7%)	0.05**
Hypertension	9 (13.8%)	5 (7.7%)	0.76**
Clinical symptoms			
Fever	25 (38.5%)	28 (43.1%)	0.71**
Dyspnea	32 (49.2%)	51 (78.5%)	0.001**
Cough	38 (58.5%)	39 (60.0%)	1**
Diarrhea	3 (4.6%)	7 (10.8%)	0.32*
Blood oxygen saturation (%)	94.28 (4.8)	89.1 (9.66)	0.001***
COVID-19 outcome			
Hospitalization duration (days)	9.28 (6.84)	4.77 (4.27)	0.001***
Intubation	16 (24.6%)	0	0.01*
Mortality	8 (12.31%)	0	0.01*
ICU admission	12 (18.5%)	2 (3.1%)	0.003*

[a]Continuous values are presented as means ± SD, and categorical variables as frequency (%). *Fisher's exact test. **Chi-square (χ^2). ***Student's *t*-test.

Table IV. Maternal complications of COVID-19 in pregnant women (n = 65).

Complications	Frequency (%)
Miscarriage	3 (4.6)
Preterm birth	12 (18.46)
Cesarean section	30 (46.15)

cy cesarean sections may be considered in cases of fetal distress due to hypoxia to preserve fetal health and prevent further maternal involvement in the infection[23]. Our study also indicated that the majority of patients received anticoagulant therapy, whereas Fayazi et al[22] found that antibiotics were primarily used to treat pregnant women with COVID-19. Additionally, our study revealed a miscarriage rate of 6.4% in pregnant women with COVID-19, which is higher compared to Ismailpour Estakhri et al's[24] reported rate of 3% and Vizheh et al's[25] rate of 3.7%.

Limitations

While this study provides valuable insights into the factors influencing COVID-19 severity in women, several limitations must be acknowledged. The findings may not be generalizable to populations outside the study's specific setting or those with different demographic characteristics, healthcare systems, or levels of access to care. Additionally, the sample size and representativeness of the study population could be limited, potentially affecting the robustness and applicability of the results. The study's reliance on retrospective data collection methods may introduce biases or inaccuracies in data reporting and collection. Furthermore, despite adjustments for potential confounders, there may be unmeasured or residual confounding factors that could influence the observed associations. These limitations suggest that while the study provides important insights, caution should be exercised when interpreting the results and applying them to broader populations.

Conclusions

The study aimed to evaluate factors contributing to COVID-19 severity in women, identifying significant associations with age, urban residence, insurance status, timing of hospitalization, comorbidities, and non-pregnancy. Notably, lack of insurance was associated with a 1.9-fold higher risk of COVID-19-related hospitalization compared to having private insurance, highlighting the impact of healthcare coverage disparities on disease outcomes. Pregnant women primarily experienced mild COVID-19 symptoms, which is consistent with previous research[26]; however, a considerable number of patients underwent cesarean sections and experienced preterm births, likely due to concerns for both maternal and fetal health. Anticoagulant therapy was commonly administered in this study, contrasting with the predominance of antibiotic use reported in other studies[22]. Additionally, a significant proportion of pregnant women experienced miscarriages, aligning with findings from previous research[25]. These insights underscore the multifaceted impact of COVID-19 on pregnant women and emphasize the need for tailored interventions and comprehensive care strategies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (ethics code: IR.KMU.AH.REC.1401.298; approval date: 2023-March-11).

Informed Consent

Written informed consent was provided by the patients to receive therapy and for the publication of this study.

AI Disclosure

No artificial intelligence or assisted technologies were used in the study's production.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

Authors' Contributions

GH M and FD designed the study and gathered the data. F KR, LA, HM, H S, and IA analyzed the data. All authors discussed the results and commented on the manuscript.

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