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Comparison of in-hospital mortality of COVID-19 between pregnant and non-pregnant women infected with SARS-CoV-2: a historical cohort study

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Abstract

Objectives: This study aimed to compare pregnant and non-pregnant women infected with SARS-CoV-2 disease (COVID-19) in terms of in-hospital mortality.

Methods: This historical cohort study was conducted on hospitalized women of reproductive ages (15–49 years) infected with SARS-CoV-2 in Fars province, Iran during 15 March 2019–10 May 2021.

Results: Out of the 5,322 patients, 330 were pregnant. The fatality rate of SARS-CoV-2 was 1.2% amongst pregnant women and 3.5% amongst non-pregnant ones. Pregnant and non-pregnant women reported the same history of smoking, opium use, previous COVID-19 infection, vaccination against SARS-CoV-2, and COVID-19 symptoms ($p > 0.05$ for all). However, the pregnant women were younger and had fewer underlying diseases ($p < 0.001$ for both). The results revealed no significant difference between the two groups regarding in-hospital clinical manifestations including the number of days after the onset of COVID-19 symptoms, mechanical ventilation, and long involvement (cRR; 95% CI=0.99 (0.96–1.02), 1.18

(0.72–2.02), and 0.95 (0.88–1.02), respectively). Nonetheless, Intensive Care Unit (ICU) admission was significantly higher in pregnant women (cRR; 95% CI=2.37(1.85–3.02)). After adjusting for age, history of underlying diseases, and ICU admission, pregnant women showed lower in-hospital mortality due to COVID-19 compared to non-pregnant women (aRR; 95% CI=0.32 (0.12–0.87)).

Conclusions: Based on the current study findings, pregnant women showed lower in-hospital mortality due to COVID-19 compared to non-pregnant ones. Nevertheless, they should follow the same recommendations as non-pregnant women, avoiding exposure to the virus and receiving medical treatment and vaccination. Further studies are recommended to address the follow-up of recovered pregnant women, their babies, and puerperium.

Keywords: COVID-19; hospitalization; mortality; pregnancy.

Introduction

World Health Organization (WHO) announced the identification of Severe Acute Respiratory Syndrome Corona Virus type 2 (SARS-CoV-2) that caused Corona Virus Disease-2019 (COVID-19) in 2020 [1, 2]. Up to 17 September 2021, Iran was ranked 8th regarding the number of confirmed cases and 11th concerning the number of deaths (<https://covid19.who.int>).

Pregnancy is a susceptible period of every woman's life; however, there are still controversies regarding maternal mortality due to COVID-19 [3–7]. Older age and history of underlying diseases are among the confirmed risk factors of COVID-19 mortality [8, 9]. This study aimed to compare hospitalized pregnant and non-pregnant women infected with SARS-CoV-2 regarding the mortality rate of COVID-19.

Materials and methods

Study participants/design

A total of 32,315 hospitalized laboratory-confirmed SARS-CoV-2 cases were reported to the Medical Care Monitoring Center (MCMC) affiliated

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to Shiraz University of Medical Sciences from 26 cities in Fars province, Iran during 15 March 2019–10 May 2021. Among these cases, 5,322 were in the reproductive ages; i.e., 15–49 years. Initially, a questionnaire was completed for all the participants, which included comprehensive information on their demographic characteristics, COVID-19 symptoms, and history of underlying diseases. It is worth mentioning that the pregnant women were hospitalized due to COVID-19 infection and not delivery issues.

This study followed a historical cohort design, in which the starting point was the first exposure to pregnancy. It continued until the last follow-up, in which the patient either died due to COVID-19 or survived.

Variable definition

Laboratory-confirmed SARS-CoV-2 cases were the positive cases confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR). Demographic characteristics included age (year), history of smoking (patients' self-report of routine and current cigarette smoking; yes/no), history of opium use (patients' self-report of routine and current opium use; yes/no), history of previous COVID-19 infection (SARS-CoV-2 infection before the study; yes/no), vaccination against SARS-CoV-2 (having been vaccinated before the study; yes/no), COVID-19 symptoms (symptomatic in case of occurrence of any symptoms (fever, cough, muscular pain, respiratory distress, loss of consciousness, loss of sense of smell, loss of sense of taste, convulsion, gastric pain, nausea, vomiting, diarrhea, anorexia, headache, vertigo, paresis, plegia, chest pain, and skin lesion)/asymptomatic), and history of underlying diseases (presence of any chronic diseases (diabetes mellitus, cancer, chronic liver disease, chronic blood disease, immune deficiency, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), cardiovascular disease, chronic renal failure, dialysis status, chronic respiratory syndrome, asthma, chronic pulmonary disease, chronic nervous disease, and hypertension (HTN)); yes/no). COVID-19 clinical manifestations included ICU admission, mechanical ventilation, long involvement, death (yes/no), and number of days after the onset of COVID-19 symptoms.

Ethical statement

All the study stages including data collection and analysis and reporting the results were in accordance with the standards approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.1165). The data were analyzed anonymously and the results were reported to the study participants.

Statistical analysis

Mean $\pm$ SD and median (Q1, Q3) were used to describe the quantitative variables and frequency (relative frequency) was used for qualitative ones. Chi-square test, crude and adjusted risk ratios, and 95% confidence intervals (CIs) were calculated using modified Poisson regression. Risk ratios were adjusted for age, history of underlying diseases, and ICU admission, which showed to be significant in univariate analysis. All analyses were performed using R 3.1.0 software and the significance level was set at 0.05.

National guidelines for the hospitalization and therapy regimes in cases of SARS-CoV-2 infection

Iranian national guidelines for COVID-19 was initially approved by the National Corona Virus Crisis Committee in January 2020 (<https://sums.ac.ir/page-rightcorona/fa/458/form/pld55727>). It focused on the diagnosis and therapy regimes of the outpatient and hospitalized infected individuals in rural and urban areas and was modified based on the number of hospitalizations and medications used in nine editions. It included flowcharts for children, pulmonary infection, medication, ICU admission, dentistry, isolation, maternal-fetal surveillance, heart surgery, screening and surveillance, death certificate, chronic obstetric pulmonary disease, plasma therapy, medical facility and staff, cancer and bone marrow transplant, special and rare diseases, and pregnancy during the epidemic. Pregnancy flowchart included case definition, disease phases, perinatal complications, and therapy regimes for outpatient and hospitalized patients. The therapy regimes included antiviral therapy such as Remdesivir in hospitalized women (200 mg IV for day one and 100 mg IV for five days). In case of kidney and liver failures, the therapy regime would be consulted fully.

Results

Among the 32,315 laboratory-confirmed SARS-CoV-2 cases reported to the MCMC, 48.5% (15,682/32,315) were female and 51.5% (16,633/32,315) were male. The proportion of SARS-CoV-2 infected females was significantly lower compared to the infected males (z -statistics=5.4, $p<0.001$). Among the 15,682 female cases, 34% (5,322/15,682) aged 15–49 years. Additionally, 6.2% (330/5,322) were pregnant and 93.8% (4,992/5,322) were not. The baseline features including demographic characteristics, COVID-19 symptoms, and history of underlying diseases for 5,322 SARS-CoV-2 infected women aged 15–49 years by pregnancy status have been compared in Table 1.

Based on the results, the pregnant women were significantly younger than non-pregnant ones ($p<0.001$). However, the two groups were similar regarding the history of smoking, opium use, previous COVID-19 infection, COVID-19 symptoms, and vaccination against SARS-CoV-2 ($p=0.37$, 0.27, 0.58, 0.62, and 0.53, respectively). Pregnant and non-pregnant women also reported similar frequencies of cough, muscular pain, loss of consciousness, loss of sense of smell, loss of sense of taste, convulsion, gastric pain, diarrhea, paresis, plegia, and skin lesions ($p=0.27$, 0.43, 0.08, 0.76, 0.14, 0.62, 0.25, 0.29, 0.2, 0.49, and 0.3, respectively). However, fever, respiratory distress, nausea, vomiting, anorexia, headache, vertigo, and chest pain were significantly less frequent in the pregnant women ($p=0.002$, <0.001 , 0.001, 0.01, 0.001, <0.001 , 0.009, and 0.01, respectively).

The results indicated that the pregnant women were less likely to develop underlying diseases ($p<0.001$).

Table 1: The demographic characteristics, COVID-19 symptoms, and underlying diseases among the 5,322 hospitalized SARS-CoV-2 infected women aged 15–49 years by pregnancy status (south of Iran, 15 March 2019–10 May 2021).

Characteristics		Pregnancy status, n (%)		p-Value
		Non-pregnant women, 4,992 (93.8%)	Pregnant women, 330 (6.2%)	
Age, years, mean $\pm$ SD		37 $\pm$ 7	30 $\pm$ 5	<0.001
History of smoking	Yes	12 (0.20%)	0 (0%)	0.37
History of opium use	Yes	21 (0.40%)	0 (0%)	0.27
History of previous COVID-19 infection	Yes	128 (3.50%)	8 (2.80%)	0.58
Vaccination against SARS-CoV-2	Yes	8 (1.40%)	0 (0%)	0.53
COVID-19 symptoms ^a	Symptomatic	4,864 (97.40%)	323 (97.90%)	0.62
Reported symptoms				
Fever	Yes	1814 (36.30%)	92 (27.90%)	0.002
Cough	Yes	2,716 (54.40%)	169 (51.20%)	0.27
Muscular pain	Yes	1984 (39.70%)	124 (37.60%)	0.43
Respiratory distress	Yes	2,591 (51.90%)	129 (39.10%)	<0.001
Loss of consciousness	Yes	73 (1.50%)	1 (0.30%)	0.08
Loss of sense of smell	Yes	165 (3.30%)	12 (3.60%)	0.76
Loss of sense of taste	Yes	104 (2.10%)	3 (0.90%)	0.14
Convulsion	Yes	9 (0.20%)	1 (0.30%)	0.62
Gastric pain	Yes	124 (2.50%)	5 (1.50%)	0.25
Nausea	Yes	521 (10.70%)	16 (4.90%)	0.001
Vomiting	Yes	277 (5.70%)	8 (2.40%)	0.01
Diarrhea	Yes	209 (4.30%)	10 (3.10%)	0.29
Anorexia	Yes	461 (9.40%)	13 (4%)	0.001
Headache	Yes	796 (16.40%)	27 (8.30%)	<0.001
Vertigo	Yes	243 (5%)	6 (1.80%)	0.009
Paresis	Yes	24 (0.50%)	0 (0%)	0.2
Plegia	Yes	7 (0.10%)	0 (0%)	0.49
Chest pain	Yes	242 (5%)	6 (1.80%)	0.01
Skin lesion	Yes	5 (0.10%)	1 (0.30%)	0.3
History of underlying diseases ^b	Yes	1,589 (31.80%)	48 (14.5%)	<0.001
Known underlying diseases				
Diabetes mellitus	Yes	370 (7.40%)	16 (4.80%)	0.08
Cancer	Yes	67 (1.30%)	1 (0.30%)	0.1
Chronic liver disease	Yes	34 (0.70%)	1 (0.30%)	0.4
Chronic blood disease	Yes	28 (0.60%)	1 (0.30%)	0.54
Immune deficiency	Yes	58 (1.20%)	0 (0%)	0.04
HIV/AIDS	Yes	5 (0.10%)	0 (0%)	0.65
Cardiovascular disease	Yes	147 (2.90%)	3 (0.90%)	0.03
Chronic renal failure	Yes	60 (1.20%)	1 (0.30%)	0.14
Dialysis status	Yes	31 (51.70%)	1 (100%)	0.34
Chronic respiratory syndrome	Yes	172 (3.40%)	2 (0.60%)	0.005
Asthma	Yes	132 (2.60%)	2 (0.60%)	0.02
Chronic pulmonary diseases	Yes	42 (0.80%)	0 (0%)	0.09
Chronic nervous disease	Yes	62 (1.20%)	1 (0.30%)	0.13
HTN	Yes	354 (7.10%)	4 (1.20%)	<0.001

HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; HTN, hypertension; SD, standard deviation. ^aSymptom status was classified as symptomatic if any of the following symptoms was reported: fever, cough, muscular pain, respiratory distress, loss of consciousness, loss of sense of smell, loss of sense of taste, convulsion, gastric pain, nausea, vomiting, diarrhea, anorexia, headache, vertigo, paresis, plegia, chest pain, and skin lesion. ^bHistory of underlying diseases was classified as known underlying diseases if any of the following clinical conditions was noted: diabetes mellitus, cancer, chronic liver disease, chronic blood disease, immune deficiency, cardiovascular disease, chronic renal failure, chronic respiratory syndrome, chronic nervous disease, and HTN. Bold values indicate the statistical significance.

Nonetheless, the two groups were similar regarding diabetes mellitus, cancer, chronic liver disease, chronic blood disease, HIV/AIDS, chronic renal failure, dialysis status, chronic pulmonary diseases, and chronic nervous disease

($p=0.08, 0.1, 0.4, 0.54, 0.65, 0.14, 0.34, 0.09$, and 0.13 , respectively). However, immune deficiency, cardiovascular diseases, chronic respiratory syndrome, asthma, and HTN were less frequent among the pregnant women

($p=0.04$, 0.03 , 0.005 , 0.02 , and <0.001 , respectively). It should be noted that according to the utilized data, it could not be determined whether the present chronic underlying diseases were associated with pregnancy or not (e.g., gestational diabetes or gestational hypertension).

The fatality rates of COVID-19 were found to be 3.5% (174/4,992) in non-pregnant women and 1.2% (4/330) in pregnant ones.

Clinical manifestations including number of days after the onset of COVID-19 symptoms, ICU admission, mechanical ventilation, long involvement, and death among the 5,322 15–49-year-old women infected with SARS-CoV-2 by pregnancy status have been presented in Table 2.

Univariate analysis results

Pregnant women were similar to non-pregnant women regarding the number of days after the onset of COVID-19 symptoms, mechanical ventilation, and long involvement ($p=0.4$, 0.48 , and 0.71). However, pregnant women were significantly more likely to be admitted in ICU ($p<0.001$). In addition, death rate was significantly lower in pregnant women ($p=0.03$).

Multiple analysis

The results of multiple analysis assessing the in-hospital mortality due to COVID-19 amongst 330 pregnant and 4,992 non-pregnant women infected with SARS-CoV-2 have been presented in Table 3. After adjusting for age, history of underlying diseases, and ICU admission, a lower rate of in-hospital death was observed among the pregnant women compared to the non-pregnant ones ($p=0.02$).

Table 3: Comparison of 330 pregnant and 4,992 non-pregnant women infected with SARS-CoV-2 regarding the in-hospital mortality of COVID-19 (south of Iran, 15 March 2019–10 May 2021).

Outcomes	Multiple analysis ^a	
	p-Value	aRR (95% CI)
Pregnancy	0.02	0.32 (0.12–0.87)
History of underlying diseases	<0.001	5.01 (3.6–6.98)
ICU admission	<0.001	12.33 (9.19–16.58)
Age	0.08	1.02 (0.99–1.04)

^aAdjusted for age, history of underlying diseases, and ICU admission; no underlying disease and no ICU admission were the reference categories. ICU, intensive care unit; aRR, adjusted rate ratio.

Discussion

The fatality rate of COVID-19 was 1.2% and 3.5% in hospitalized SARS-CoV-2-infected pregnant and non-pregnant women, respectively. Hospitalized pregnant women were similar to non-pregnant ones regarding the history of smoking, opium use, previous COVID-19 infection, vaccination against SARS-CoV-2, and COVID-19 symptoms. However, they were significantly younger and had fewer underlying diseases. The two groups were also similar in terms of cough, muscular pain, loss of consciousness, loss of sense of smell, loss of sense of taste, convulsion, gastric pain, diarrhea, paresis, plegia, and skin lesions. However, fever, respiratory distress, nausea, vomiting, anorexia, headache, vertigo, and chest pain were significantly less frequent in the pregnant women. Moreover, the two groups were homogeneous concerning the frequency of underlying diseases including diabetes mellitus, cancer, chronic liver disease, chronic blood disease, HIV/AIDS, chronic renal failure, dialysis status, chronic pulmonary diseases, and chronic nervous disease. Nonetheless, immune

Table 2: Number of days after the onset of COVID-19 symptoms, ICU admission, mechanical ventilation, long involvement, and death among the 5,322 hospitalized SARS-CoV-2 infected women aged 15–49 years by pregnancy status (south of Iran, 15 March 2019–10 May 2021).

Clinical manifestations		Pregnancy status		Univariate analysis
		No pregnant women, n=4,992 (93.8%)	Pregnant women, n=330 (6.2%)	cRR ^a (95% C.I.)
Number of days after the onset of COVID-19 symptoms (day), median (Q1, Q3)		6 (3,8)	5(3,8)	0.99(0.96–1.02)
ICU admission, n (%)	Yes	390 (7.8%)	61 (18.5%)	2.37 (1.85–3.02)
Mechanical ventilation, n (%)	Yes	188 (3.8%)	15 (4.5%)	1.18 (0.72–2.02)
Long involvement, n (%)	Involved	3,241 (96.5%)	56 (91.8%)	0.95 (0.88–1.02)
Death, n (%)	Death	174 (3.5%)	4 (1.2%)	0.35 (0.13–0.94)

^acRR, crude risk ratio; ICU, intensive care unit. Bold values indicate the statistical significance.

deficiency, cardiovascular disease, chronic respiratory syndrome, asthma, and HTN were significantly less frequent amongst the pregnant women, which implied that pregnancy was followed by a healthier life. It was also shown that hospitalized pregnant women infected with SARS-CoV-2 were more likely to receive ICU admission compared to non-pregnant ones. However, no differences were detected between the two groups regarding the number of days after the onset of COVID-19 symptoms, mechanical ventilation, and long involvement. After adjusting for age, history of underlying diseases, and ICU admission, a lower in-hospital death was seen in pregnant women compared to non-pregnant ones. Nevertheless, they had to follow the same recommendations as non-pregnant women including avoiding exposure to the virus and receiving medical treatment and vaccination. Yet, further studies are required to address the follow-up of recovered pregnant women, their babies, and puerperium.

The current study estimated a lower rate of in-hospital fatality for COVID-19 in comparison to SARS and MERS (1.2% vs. 25.8 and 28.6%) during pregnancy [2]. In parallel to the current findings, in-hospital fatality rate of COVID-19 was reported to be lower in pregnant women than in non-pregnant ones (0.8% vs. 3.5%) in the USA [10].

Previously, symptomatic pregnant women with COVID-19 reported similar frequencies of cough and respiratory distress to their non-pregnant counterparts. Nonetheless, headache, muscle pain, fever, and diarrhea were reported to be less frequent [8, 11, 12]. In the current study, however, the frequency of cough, muscle pain, and diarrhea was the same in the two groups, while headache, respiratory distress, and fever were significantly less frequent among the pregnant women. However, one study done in Egypt reported no significant difference between the two groups in this regard [13]. Diabetes mellitus and cardiovascular diseases were among the most important comorbidities responsible for death due to COVID-19 during pregnancy [2, 14, 15]. Nevertheless, the current study findings indicated that the frequency of diabetes mellitus was the same in the two groups and cardiovascular diseases were significantly less frequent among the pregnant women.

Two confirmed risk factors in pregnancy were higher age and underlying diseases [16, 17], which was in line with the risk factors detected in the current investigation.

Regarding the in-hospital clinical manifestations of COVID-19 in pregnancy, some studies revealed that hospitalized pregnant women had a higher odds of ICU admission compared to non-pregnant ones [8, 18], which was in agreement with the current study findings. Other studies also reported similar mechanical ventilation in the

two groups [13, 18, 19]. Some studies, however, reported a higher rate of mechanical ventilation [8, 19].

There are discrepancies regarding the effect of SARS-CoV-2 infection on maternal mortality. The association has been shown to diverge based on the adjusted risk factors in the model. Some studies have reported higher mortality rates in pregnant women compared to non-pregnant ones. For instance, one systematic review and meta-analysis including 31,469 women reported a higher rate of maternal mortality adjusting on mechanical ventilation. A cohort study on 10,366 women also revealed a higher rate of maternal mortality adjusting on background demographic and medical factors. Finally, a historical cohort study including 240 pregnant women reported that the in-hospital fatality rate was 13.6 folds higher in pregnant women [8, 18, 20, 21]. However, some studies have reported no significant association between the pregnancy status and in-hospital death due to COVID-19. As an example, a cohort study including 64 pregnant women done in Egypt revealed the same crude odds of death in pregnant women. Another historical cohort study including 22,493 women in the USA showed the same mortality after adjusting for comorbidities and age. A systematic review and meta-analysis including 31,710 women also reported the same mortality rates adjusting on comorbidities and age [8, 13, 19]. Some studies, however, have indicated a lower rate of in-hospital death due to COVID-19 in pregnant women compared to non-pregnant ones. For example, a historical cohort study including 1,062 pregnant and 9,815 non-pregnant ones in the USA demonstrated substantially lower rates of in-hospital mortality within the ICU admitted group. Another historical cohort study including 97,712 women in Brazil revealed that pregnant women had a lower risk of in-hospital mortality after adjustment for sociodemographic factors, epidemiological characteristics, and comorbidities. They concluded that pregnancy appeared to have a favorable effect on SARS-CoV-2 infection [10, 22]. In addition, some systematic reviews and meta-analyses have reported lower rates of maternal mortality due to COVID-19 [7, 8, 22, 23].

A prior epidemiological study revealed that female gender was 50% less likely to expire due to COVID-19 in comparison to male gender [18]. Accordingly, females in the reproductive ages (15–49 years) experienced a 60% decline in severe clinical manifestations compared to their aged-matched males in the control group [18, 24]. Generally, the immunological response to SARS-CoV-2 infection relies on the appropriate function of the immune system; the immune system adapts during pregnancy to allow for the implantation and growth of the semi-allogenic fetus [25–27]. The altered immune response during pregnancy may be partially induced by the inflammatory response to

the pathogenesis of infection as well as by the circulating progesterone that has immuno-modulatory properties [28]. Progesterone also has the ability to repair damages caused by viruses [29]. Considering no intra-uterine transmission for SARS-CoV-2 [3, 7, 30, 31], both the infected mother and her healthy fetus may fight against SARS-CoV-2. The abovementioned reasons alongside the fact that the pregnant women were found to be younger and healthier and had no physiological problems can justify the lower mortality rate of COVID-19 in pregnant women compared to their non-pregnant counterparts.

Strengths and limitations

Body mass index (BMI) has been reported as one of the important determinants of survival in SARS-CoV-2 infected patients. In a study done in South Korea, it was revealed that BMIs ≥ 25.0 kg/m² and < 18.5 kg/m² were associated with an increased fatality due to COVID-19, illustrating the importance of maintaining a healthy normal weight ($18.5 < \text{BMI} < 25$ kg/m²) during the COVID-19 pandemic [32]. In some studies including a systematic review and meta-analysis, BMI > 30 kg/m² was associated with an increased risk of death due to COVID-19 in hospitalized pregnant women [8, 33]. As a limitation of the current work, however, data on the patients' BMI were unavailable to assess. In addition, Center for Disease Control and Prevention (CDC) recommended urgent action to increase COVID-19 vaccination for all the people aged over 12 years, especially pregnant women, in order to prevent serious illnesses, death, and adverse pregnancy outcomes [34–36]. However, as another study limitation, the reported vaccination rate was extremely low and no data were available on the partial or full vaccination status of the participants, because there was no mass vaccination plan up to the study period. It has been suggested that the benefits of receiving a COVID-19 vaccine outweigh any known or potential risks of vaccination during pregnancy. In fact, none of the COVID-19 vaccines contain live virus and cannot make anyone sick. Early data have also proved the safety of receiving an mRNA COVID-19 vaccine (Moderna or Pfizer-BioNTech) during pregnancy [37], without any risk of miscarriage. They reduced the risk of infection, as well [38, 39]. Finally, pregnant women are recommended to get a booster shot to obtain the highest protection [35]. However, there is still call for further investigations in this area [40]. Since a considerable proportion of complications occur in the puerperal period, as another limitation, no post-partum information was provided to be addressed in the research,

One of the strength of this study was the use of a large database including the data released from 44 boarding centers affiliated to MCMC from 26 cities of the province. In addition, it was a hospital-based database that provided a clearly defined population.

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Author contribution: Mahsa Akbari prepared the data, interpreted the results, and wrote the draft. Mohammad javad Moradian developed the theoretical formalism, and interpreted the results. Marjan Zare, Alireza Mirahmadizadeh, Mahsa Akbari, and Mohammad javad Moradian approved the final version of the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: All the study stages including data collection and analysis and reporting the results were in accordance with the standards approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.1165). The data were analyzed anonymously and the results were reported to the study participants.

Data availability: The data set generated during the current study is not publicly available due to confidentiality of the patient's information; however, are available from the corresponding author on reasonable request. The work is done and support in Shiraz University of Medical Sciences, Shiraz, Iran.

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