



Remdesivir in pregnant women with moderate to severe coronavirus disease 2019 (COVID-19): a retrospective cohort study

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Abstract

Data on the efficacy of remdesivir in Coronavirus Disease 2019 (COVID-19) are limited in pregnant patients since they have been excluded from clinical trials. We aimed to investigate some clinical outcomes following remdesivir administration in pregnancy. This was a retrospective cohort study conducted on pregnant women with moderate to severe COVID-19. The enrolled patients were divided into two groups with and without remdesivir treatment. The primary outcomes of this study were the length of hospital and intensive care unit stay; respiratory parameters of hospital day 7 including respiratory rate, oxygen saturation, and mode of oxygen support; discharge until days 7 and 14, and need for home oxygen therapy. Secondary outcomes included some maternal and neonatal consequences. Eighty-one pregnant women (57 in the remdesivir group and 24 in the non-remdesivir group) were included. The two study groups were comparable according to the baseline demographic and clinical characteristics. Of the respiratory outcomes, remdesivir was significantly associated with a reduced length of hospital stay ($p = 0.021$) and also with a lower level of oxygen requirement in patients on low-flow oxygen [odds ratio (OR) 3.669]. Among the maternal consequences, no patients in the remdesivir group developed preeclampsia but three patients (12.5%) experienced this complication in the non-remdesivir group ($p = 0.024$). Furthermore, in patients with moderate COVID-19, the percentage of emergency termination was significantly lower in remdesivir group (OR 2.46). Our results demonstrated some probable benefits of remdesivir in respiratory and also maternal outcomes. Further investigations with a larger sample size should confirm these results.

Keywords COVID-19 · Pregnancy · Remdesivir · Respiratory parameters · Preeclampsia

Introduction

Coronavirus Disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and has affected more than 623 million individuals worldwide according to the data from the World Health Organization (WHO) as of October 13, 2022 [1]. Since the onset of the COVID-19 pandemic, several pharmacological treatments have been introduced using drug repurposing and have shown promising results for the treatment of moderate to severe cases [2]. SARS-CoV-2 uses RNA-dependent RNA polymerase (RdRp) for replication, and remdesivir, a nucleotide analog, inhibits the SARS-CoV-2 replication via selective suppression of viral RdRp in vitro [3, 4]. Over the past 2 years, several studies and trials have demonstrated the efficacy of remdesivir treatment in non-pregnant adults with severe COVID-19 [5, 6]. However, studies such as the WHO

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Solidarity trial have reported that remdesivir had no effect on the length of hospital stay or survival compared with the standard of care [7]. Other trials have yielded equivocal results regarding the effects of remdesivir [8, 9].

Pregnant patients are more vulnerable to severe or critical features of COVID-19 [10]. For instance, the risk of intensive care unit (ICU) admission and the need for mechanical ventilation is approximately two to four times higher among pregnant than matched non-pregnant women [11–13]. Physiological changes in the immune and cardiovascular systems are probably the underlying reason for the increased susceptibility of pregnant women to viral respiratory infections [14]. The risk of severe disease increases especially when respiratory infection occurs in the third trimester [11–13, 15]. In addition, pregnancy outcomes could be impacted by COVID-19, resulting in the higher rates of preterm birth and cesarean section [16]. Data on the administration of remdesivir in COVID-19 pregnant patients are scarce since pregnant women have been excluded from clinical trials of remdesivir. Nonetheless, Remdesivir was authorized in pregnant women with severe COVID-19 as of March 21, 2020, through a compassionate-use program [10]. In this retrospective cohort study, we aimed to explore the association between remdesivir and pregnancy outcomes in patients with moderate to severe COVID-19.

Methods

Study design and participants

This was a retrospective cohort study conducted on a group of pregnant women with moderate to severe COVID-19 hospitalized in the four affiliated hospitals of Shahid Beheshti University of Medical Sciences from September 2020 to March 2022. The study protocol was approved by the Institutional Review Board (IRB) and adhered to the ethical principles outlined in the Declaration of Helsinki. All patients were provided with informed consent to use the de-identified data.

Study inclusion criteria were: (1) pregnant women with polymerase chain reaction (PCR) confirmed COVID-19 and (2) moderate to severe COVID-19 pneumonia. The following classification was used to categorize patients into moderate and severe COVID-19 [17, 18]:

- Moderate: (1) presence of respiratory symptoms (including shortness of breath, feeling of pain and pressure in chest) with or without fever (Body temperature $38^{\circ}\text{C} \leq$, (2) oxygen saturation $\geq 94\%$, or (3) lung involvement less than 50% on imaging
- Severe: (1) tachypnea (respiratory rate > 30 breaths per minute), (2) hypoxia (oxygen saturation $< 94\%$ on room

air or $\text{PaO}_2/\text{FiO}_2$ (partial pressure of oxygen in the arterial blood to fractional inspired oxygen) < 300 mmHg), or (3) $> 50\%$ lung involvement on imaging.

Exclusion criteria were: (1) administration of remdesivir after 2 days of hospitalization in the remdesivir group, (2) multiple-pregnancy, (3) creatinine clearance less than 30 ml/min, (4) aspartate transaminase (AST) or alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN), (5) multi-organ failure, (6) history of obstructive or restrictive lung disease, (7) receiving other anti-viral agents such as Tocilizumab (8) patients not receiving corticosteroids (due to probable effect of corticosteroids on disease course, all included patients had received corticosteroids).

Data and outcomes

The required data were extracted from the electronic medical records of four hospitals. These data included maternal age, gestational age, gravidity and parity, past medical history, signs and symptoms of COVID-19, respiratory parameters, and laboratory measurements (Tables 1, 2, 3). As receiving or not receiving remdesivir was the main predictor variable of the study, the included patients were categorized into two groups with and without remdesivir treatment.

Intravenous (IV) remdesivir was administered 200 mg as a single dose on day 1, followed by 100 mg once daily for 5 days, within 48 h of hospitalization for the remdesivir group. Note that remdesivir was provided by the same company for all patients in the affiliated hospitals.

Table 1 Baseline demographic and clinical characteristics of pregnant patients with and without remdesivir on admission day

	Remdesivir group (n = 57)	Non-remdesivir group (n = 24)	p value
Maternal age (year)	33.19 (5.40)	31.88 (4.36)	0.294
Gestational age (week)	28.51 (7.28)	27.73 (8.79)	0.680
Gestational trimester			0.232
1	3 (5.3%)	4 (16.7%)	
2	19 (33.3%)	8 (33.3%)	
3	35 (61.4%)	12 (50%)	
Gravidity	2.53 (1.29)	2.71 (2.09)	0.635
Parity	1.18 (0.98)	1.29 (1.87)	0.716
Past medical history			
Gestational diabetes	16 (28.1%)	7 (29.2%)	0.920
Preexisting diabetes	2 (3.5%)	0 (0%)	0.999
Chronic hypertension	1 (1.8%)	2 (8.3%)	0.208
Thyroid disease	13 (22.8%)	11 (45.8%)	0.038
Cardiac disease	2 (3.5%)	0 (0%)	0.999

Table 2 COVID-19-related and respiratory characteristics of pregnant patients with and without remdesivir

	Remdesivir group (n = 57)	Non-remdesivir group (n = 24)	p value
Duration of symptoms before admission	8.38 (2.84)	7.12 (3.08)	0.123
Fever/chills	39 (68.4%)	17 (70.8%)	0.830
Cough	54 (94.7%)	21 (87.5%)	0.256
Shortness of breath	42 (73.7%)	21 (87.5%)	0.172
Myalgia	30 (52.6%)	13 (54.2%)	0.899
Headache	7 (12.3%)	7 (29.2%)	0.105
Anosmia	7 (12.3%)	3 (12.5%)	0.999
Sore throat	8 (14%)	2 (8.3%)	0.715
Runny nose	2 (3.5%)	0 (0%)	0.999
Nausea/vomiting	8 (14%)	5 (20.8%)	0.513
Diarrhea	4 (7%)	4 (17.4%)	0.218
Contact with COVID-19 patients	33 (70.2%)	7 (70%)	0.999
Severity of COVID-19			0.083
Moderate	31 (54.4%)	18 (75%)	
Severe	26 (45.6%)	6 (25%)	
Respiratory rate on admission day	26.05 (7.23)	25.38 (6.17)	0.690
Oxygen saturation on admission day	92.74 (3.56)	93 (3.16)	0.755
Mode of oxygen support on admission day			0.811
Low-flow oxygen	34 (59.6%)	15 (62.5%)	
High-flow oxygen	23 (40.4%)	6 (37.5%)	

Table 3 Laboratory findings of pregnant patients with and without remdesivir

	Remdesivir group (n = 57)	Non-remdesivir group (n = 24)	p value
White blood cell count on admission day, 10^3 cells per mL	7600 (2887.5)	6829.1 (2443.7)	0.258
Minimal hemoglobin level, g/dl	10.91 (14.5)	10.47 (1.94)	0.263
Anemia during admission ^a	15 (26.3%)	12 (50%)	0.069
Minimal platelet count, 10^9 cells per L	182.3 (58.4)	186.9 (67.4)	0.762
Thrombocytopenia during admission ^b	5 (8.8%)	3 (12.5%)	0.608
Maximal D-dimers, μ g/L	1376.6 (1207)	2432.5 (2270.1)	0.084
Maximal Erythrocyte sedimentation rate, mm/hr	51.49 (19.70)	54.15 (20.18)	0.611
Maximal C-reactive protein, mg/L	61.88 (36.24)	45.72 (48.25)	0.124
Maximal aspartate aminotransferase, U/L	75.26 (73.82)	147.01 (310.13)	0.284
Maximal alanine aminotransferase, U/L	71.02 (86.89)	150.27 (370.17)	0.320
Maximal creatininaemia, mg/dl	0.75 (0.13)	0.80 (0.22)	0.222
Maximal procalcitonin, g/mL	0.18 (0.54)	0.23 (0.41)	0.845
Maximal Interleukin-6, pg/ml	39.07 (45.20)	17.40 (17.81)	0.519
24-h Urine Protein, mg/day	770.43 (369.97)	452.29 (191.41)	0.066
Maximal ferritin, mg/L	133.04 (90.17)	245.26 (398.0)	0.281
Maximal Lactate dehydrogenase, IU/L	638.27 (268.75)	594.31 (362.66)	0.567
Maximal Troponin I, ng/ml	0.06 (0.10)	0.04 (0.07)	0.497

^aAnemia: Hg < 10 gr/dl^bThrombocytopenia: platelet < 100×10^9 /liter

Corticosteroids were initiated in the 24 to 48 h following hospitalization. According to the national protocol, dexamethasone was given intravenously/orally (6 mg/day) or

prednisolone orally (40 mg/day) for 10 days or till discharge. If the gestational age was between 24 and 33 weeks and 6 days, a therapeutic dose of corticosteroid was administered

for the maturation of fetal lungs (dexamethasone: 4 doses of intramuscular (IM) 6 mg every 12 h or betamethasone: 2 doses of IM 12 mg every 24 h).

Pharmacological thromboprophylaxis with enoxaparin or unfractionated heparin (UFH) was conducted in those without anticoagulant contraindication as per the national protocol.

The primary outcome measures of this study were the length of hospital and ICU stay, respiratory rate on day 7, oxygen saturation on day 7, mode of oxygen support on day 7, hospital discharge until day 7 and day 14; and the need for home oxygen therapy. The secondary outcome measures of the study were maternal and neonatal outcomes, which are listed in Table 4.

Statistical analysis

The Statistical Package of Social Science Software (SPSS version 20, IBM Company, USA) and R software (version 4.2.2) were used for data analysis. Categorical and continuous variables were demonstrated as frequency (percent) and mean (standard deviation), respectively. Student t-test

(two-tailed) was used to compare the continuous variables between the remdesivir and non-remdesivir groups. The Chi-square test or Fisher's exact test was used for the comparison of categorical variables.

We considered some variables as confounders in regression analyses, including maternal age, gestational trimester, and COVID-19 severity.

Poisson regression was used to evaluate the association between receiving remdesivir and the length of hospital stay (in day). A negative binomial regression was carried out to investigate receiving remdesivir and the length of ICU stay (in day) association. Exponentiated coefficients (incidence rate ratio (IRR) and 95% confidence interval (CI)) were estimated for each model. Linear regression analysis was done to assess the association between receiving remdesivir and respiratory rate on day 7 or oxygen saturation on day 7.

As the sample size was sparse, a Bayesian approach was applied to analyze the categorical outcomes. Therefore, a Bayesian binary or multinomial logistic regression analysis was done to investigate the correlation between receiving remdesivir and the mode of oxygen support on day 7, hospital discharge until days 7 and 14, and the need for home

Table 4 Maternal and neonatal outcomes in patients with and without remdesivir

	Remdesivir group (n = 57)	Non-remdesivir group (n = 24)	p value
Preeclampsia	0 (0%)	3 (12.5%)	0.024
New onset hypertension	1 (1.8%)	2 (8.7%)	0.197
DVT	1 (1.8%)	0 (0%)	0.999
ARDS	1 (1.8%)	0 (0%)	0.999
Amniotic fluid volume			0.527
Normal	47 (87%)	22 (91.7%)	
Oligohydramnios ^a	6 (11.1%)	1 (4.2%)	
Polyhydramnios ^b	1 (1.9%)	1 (4.2%)	
IUFD during admission	1 (1.7%)	0 (0%)	0.999
Early preterm delivery (24 to 33 ⁺ 6 weeks)	5 (10%)	3 (15%)	0.68
Late preterm delivery (34 to 36 ⁺ 6 weeks)	10 (20%)	5 (25%)	0.749
Gestational age at termination of pregnancy, weeks	37.16 (4.21)	37.61 (2.47)	0.658
Emergency termination	13 (26.5%)	6 (30%)	0.228
Route of delivery			0.906
Vaginal delivery	14 (28.6%)	6 (30%)	
Cesarean section	35 (71.4)	14 (70%)	
Birth weight, gram	2924.8 (757.5)	3040.2 (653.3)	0.553
SGA ^c	3 (6.1%)	2 (10%)	0.623
5-min Apgar score	9.51 (1.74)	9.90 (0.30)	0.327
NICU admission	17 (35.4%)	7 (35%)	0.974
Neonatal death	1 (2.1%)	1 (5%)	0.517

ARDS acute respiratory distress syndrome, DVT deep vein thrombosis, IUFD intrauterine fetal death, NICU neonatal intensive care unit, SGA small for gestational age

^aOligohydramnios refers to an amniotic fluid index (AFI) of less than 8 cm

^bPolyhydramnios refers to an AFI of more than 24 cm

^cSGA refers to a newborn < 10th percentile for birth weight for gestational age

oxygen therapy, using R package of “rstanarm” version 2.21.3., function “stan_glm”. A p value of <0.05 was considered statistically significant.

Results

Baseline demographic and clinical characteristics

We initially evaluated the electronic data of 304 pregnant patients who were admitted to our four hospitals between September 2020 and March 2022. A total of 81 pregnant women (57 in the remdesivir group and 24 in the non-remdesivir group) were included in this study. Figure 1 shows the flowchart for the analytical cohort derivation.

None of the included patients were previously vaccinated against COVID-19. Maternal age ranged from 19 to 49 years (mean: 33.19) in the remdesivir group and from 22 and 44 years (mean: 31.88) in the non-remdesivir group. Most patients were in the third trimester of pregnancy (61.4% in the remdesivir group and 50% in the

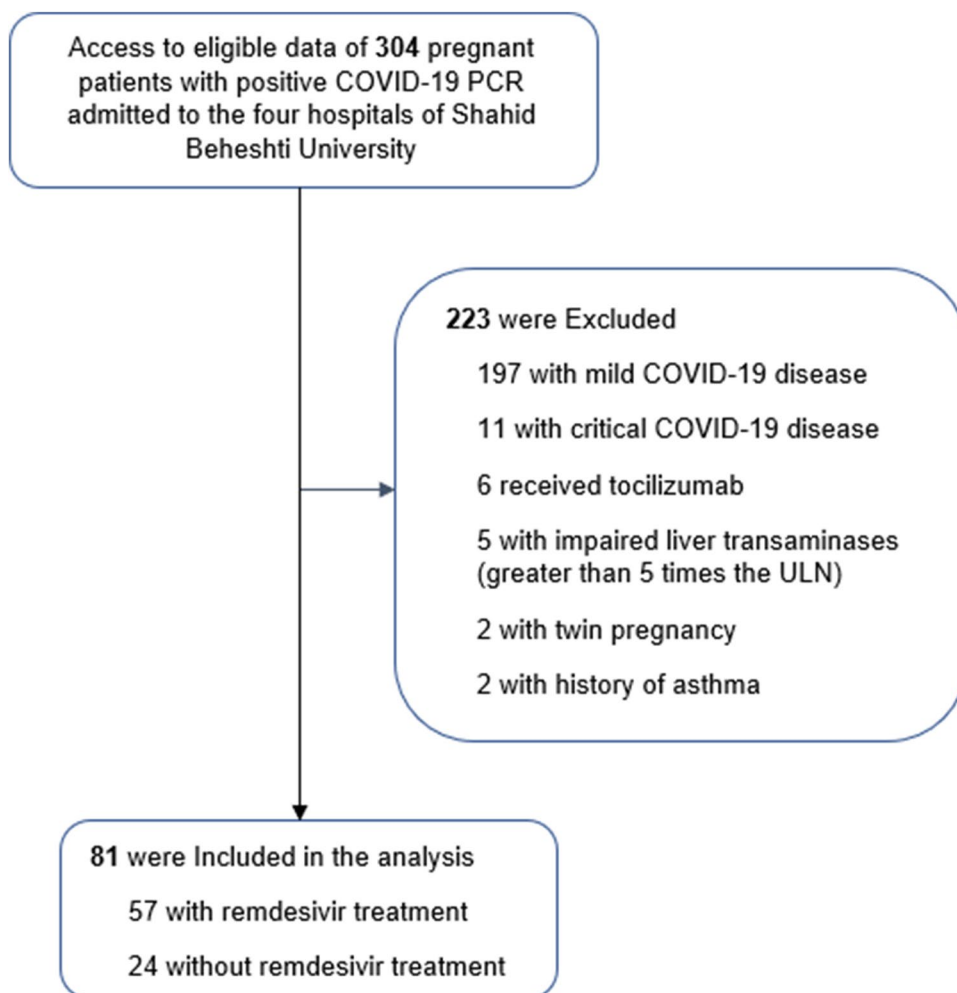
non-remdesivir group). The two study groups were comparable according to the baseline demographic and clinical characteristics (Table 1).

COVID-19 characteristics and laboratory data

As shown in Table 2, signs, symptoms, and duration of symptoms prior to admission were comparable between the two study groups. In either group, fever/chills, cough, and shortness of breath were the most frequent symptoms. The proportion of moderate and severe COVID-19 patients was comparable between the groups ($p=0.083$). In addition, there was no significant difference in respiratory parameters of the two groups, including respiratory rate, oxygen saturation, and the mode of oxygen support on the day of admission.

As shown in Table 3, the two study groups were comparable based on all laboratory measurements. Also, liver transaminase levels did not show any significant difference between the two groups.

Fig. 1 Flow chart of the final study population



Primary outcomes including clinical and respiratory parameters

Poisson regression revealed that there was a significant association between receiving remdesivir and reduced length of hospital stay (IRR = 0.791; 95% CI 0.655–0.955), (Supplementary Table 1). However, negative binomial regression and linear regression did not represent a significant association between receiving remdesivir and the length of ICU stay ($p=0.196$), respiratory rate on day 7 ($p=0.197$), and oxygen saturation on day 7 ($p=0.096$) (Supplementary Tables 2 to 4).

Bayesian binary logistic regression demonstrated a significant relationship between receiving remdesivir and hospital discharge until day 7 (odds ratio (OR) = 2.718; 95% CI 1.105–7.398) and day 14 (OR 4.953; 95% CI 1.221–22.198) (Supplementary tables 5 to 6). However, no significant association was observed between receiving remdesivir and the need for home oxygen therapy (OR 0.449; 95% CI 0.165–1.221) (Supplementary Table 7).

Moreover, the results of Bayesian multinomial logistic regression revealed that there was a significant association between receiving remdesivir and changing the level of oxygen support from low-flow oxygen on admission day to breathing in ambient air without supplemental oxygen on day 7 (Supplementary Table 8), so that those patients of remdesivir group, had a greater chance of being no longer in need of oxygen support on day 7 (OR 3.669; 95% CI 1.350–9.025).

However, such a reduction in oxygen requirement from high-flow on admission day to low-flow on day 7 was not statistically significant between the two groups (OR 1.00; 95% CI 0.247–4.055).

Secondary outcomes including maternal and neonatal findings

As shown in Table 4, Intrauterine fetal death (IUFD) occurred in only one case in the remdesivir group, but there was no maternal mortality among all patients. None of the patients in the remdesivir group developed preeclampsia; however, three patients (12.5%) in the non-remdesivir group were affected. As shown in the univariate analysis (unadjusted for confounders), the proportion of developing preeclampsia was statistically different between the two groups ($p=0.024$). Moreover, the results of Bayesian multivariate logistic regression (Supplementary Table 9) indicated a statistically significant association between receiving remdesivir and less chance of developing preeclampsia (OR 27.11; 95% CI 3.67–221.41).

Emergency termination via vaginal delivery or cesarean section was indicated in a total of 19 patients (Table 4). The percentage of emergency termination did not differ

including all patients (with moderate or severe COVID-19), but it was significantly lower in remdesivir compared with the non-remdesivir group in patients who experienced moderate Covid-19 (11.1% vs 42.9%) ($p=0.042$). Moreover, the results of Bayesian multivariate logistic regression (Supplementary Table 10) demonstrated a statistically significant association between not receiving remdesivir and the need of emergency termination in moderate COVID-19 (OR 2.27; 95% CI 1.11–6.05), so that the proportion of emergency termination was significantly lower in patients who had received remdesivir.

There was no significant difference in the percentage of oligohydramnios between the groups. Other maternal and neonatal outcomes, such as new-onset hypertension (HTN), deep vein thrombosis (DVT), acute respiratory distress syndrome (ARDS), preterm delivery, birth weight centile, 5-min Apgar score, neonatal intensive care unit (NICU) admission, and neonatal death showed no significant difference between the two groups.

Discussion

In this cohort study conducted on pregnant patients with moderate to severe COVID-19, we planned to assess some impacts of remdesivir administration within 48 h of admission. Our results demonstrated that remdesivir might reduce hospital stay and the probability of preeclampsia development, and also it can lead to a lower level of oxygen requirement in patients in need of low-flow oxygen. The other positive effect was less chance of emergency termination in patients of moderate COVID-19.

Since the onset of COVID-19 pandemic, several studies of non-pregnant population have shown inconsistent results regarding the effectiveness of remdesivir [7–9]. In addition, data on how COVID-19 is treated during pregnancy and also studies of remdesivir in this population are more limited [19].

In a multicenter observational study by Burwick et al., 86 patients, including 67 pregnant and 19 post-partum women with severe and critical COVID-19 were treated with a 10-day course of remdesivir leading to a high rate of clinical recovery. Their results revealed a reduction in the level of oxygen need in 96% of pregnant and 89% of postpartum women on day 28 of hospitalization. This effect was found in patients on any type of oxygen support from low-flow to high-flow oxygen and mechanical ventilation [10]. Note that there was no matched control group in their study. Although data on the efficacy of remdesivir is not obviously clear [7, 9, 20], recently some guidelines such as National Institutes of Health (NIH) tend to support remdesivir use in adults on no or minimal supplemental oxygen [21]. They believed that remdesivir might be less effective in more severe COVID-19

and patients on ventilatory support [9, 22]. Consistent with these recommendations, our results showed the decreased requirement of supplemental oxygen in patients who were supported with only low-flow and not high-flow oxygen.

In another study on 35 pregnant women with moderate COVID-19, Nasrallah et al. [23] reported that early administration of remdesivir within 48 h of admission led to early clinical recovery; however, delayed treatment was associated with a longer recovery as well as hospitalization. They considered recovery as discharge on day 7 or breathing in ambient air. Furthermore, all patients (17 patients) on early remdesivir treatment experienced clinical improvement on day 7, but only 3 out of 11 patients without remdesivir did [23]. In our cohort study, we excluded those who received remdesivir after 48 h of admission to overcome possible confounding effect of delayed treatment. Our finding revealed that remdesivir may reduce hospital stay and also it can lead to an earlier discharge, because our finding showed a significant correlation between receiving remdesivir and discharge till days 7 and 14.

Previous data have shown that course of COVID-19 is associated with a higher incidence of preeclampsia due to impaired renal function [24, 25]. However, no study has been reported any correlation between remdesivir and the development of preeclampsia. Our results demonstrated that remdesivir might significantly decrease the probability of preeclampsia. By consensus, in the study by Burwick et al., none of the pregnant patients experienced preeclampsia [10]. As such, the reduction in preeclampsia in patients treated with remdesivir could be due to improved renal function. Recent data on the impact of remdesivir on renal function are not completely consistent in the general population. In the Elec et al. study [26], which investigated the effect of remdesivir on patients with a history of renal transplant, they presented that remdesivir does not cause renal impairment, but also leads to increased eGFR (estimated glomerular filtration rate). On the contrary, some studies have reported the adverse role of remdesivir in renal function [27]. The favorable impact of remdesivir might be through inhibition of NF-kb (nuclear factor-kb) and MAPK (mitogen-activated protein kinase) signaling pathways and thus suppressing the expression of NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome leading to improvement lipopolysaccharide-induced acute kidney injury [28]. In contrast, a number of reports have shown that NLRP3 inflammasome is involved in the pathophysiology of preeclampsia [29–31]. It is suggested that future studies investigate the potential role of remdesivir in preventing preeclampsia in pregnant women with COVID-19.

The other finding of our study was a significantly lower chance of emergency termination in patients with moderate disease severity in remdesivir (11.1%) compared with non-remdesivir group (42.9%) (OR 2.46). More research

is needed as no previous studies have reported the such effect of remdesivir.

This study has its own strengths and limitations. Participants who were not receiving corticosteroid treatment or who had received the COVID-19 vaccine were not included in the analysis for optimal matching. We also considered some confounding factors as covariates in the analysis, including maternal age, gestational trimester, and COVID-19 severity.

There are two main limitations in this study that could be addressed in future research. The first is the relatively small sample size, even though our sample size is comparable to the literature studying related questions. Considering widespread vaccination and the reduction in moderate to severe cases of COVID-19, we were not able to increase the sample size. The second limitation is the short-term phase of evaluation of respiratory and clinical outcomes (day 7 and day 14 of hospitalization). We could nevertheless suggest some novel findings despite these restrictions. However, further research with a longer duration and a larger sample size of pregnant patients should be undertaken.

Conclusion

Our results represented that remdesivir may lead to a less hospitalization time and a reduction in oxygen need while patients are on low-flow oxygen. In regards to maternal outcomes, it might help to less probability of preeclampsia development and also a lower chance of emergent termination in moderate COVID-19. As with the majority of studies, the design of the current study is subject to limitations. We recommend that further studies with a larger sample size should verify these new findings.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10238-023-01095-0>.

Author contributions TA and MK designed the work. MMS and SO collected data. ZN, NR and FEM analyzed and interpreted data. TA and MMS wrote the initial draft of the manuscript. PP, MM and SSG edited the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets analyzed in the current study will be shared via the following e-mail address: maryam.masoumi.sh@gmail.com.

Declarations

Competing interest All authors declare that they have no potential conflicts of interest.

Ethics approval The protocol of this study was approved by the Institutional Review Board (IRB) and performed according to the ethical principles outlined in the Declaration of Helsinki.

Consent to participate All participants were provided with informed consent to use the de-identified data.

Consent to publish Patients signed informed consent regarding publishing their data.

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