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Original Research Article

Co-relation between high resolution computerised tomography (HRCT) score and effectiveness of remdesivir treatment in covid-19 positive pregnant patients

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ABSTRACT

Objective: To evaluate the effectiveness of Remdesivir in COVID-19 POSITIVE PREGNANT patients & its co-relation with their HRCT score (with abdominal lead shield) at the time of admission at our institute.
Materials and Methods: It was a retrospective observational study including 93 COVID -19 POSITIVE pregnant patients at varied weeks of gestation admitted and treated at our institute from March 2020 till June 2021. Out of these 15 patients required INTENSIVE CARE UNIT (ICU) admission due to their disease severity and received Remdesivir after physician consultation. Remaining 78 patients had HRCT SCORE of 7 or less (MILD CATEGORY) and did not require ICU admission and hence were excluded from receiving remdesivir.They were divided into 2 groups – Group A and Group B. Group A (MODERATE CATEGORY) including covid -19 positive pregnant patients with HRCT score of 8 to <17/25 had 8 patients and Group B (SEVERE CATEGORY) including covid -19 positive pregnant patients with high HRCT Score of >17/25 had 7 patients. The primary outcome was to evaluate difference in both groups for clinical improvement after 5 days of initiation of Remdisivir therapy in terms of (a) Oxygen requirement (b) Spo2 levels (c) length of hospital stay (d) Death rate (e) HRCT score on day 10 after initiation of remdesivir therapy. Secondary outcome was to evaluate side effects of the drug on the mother and its effect on the baby while in-utero and after delivery.
Results: Covid-19 positive pregnant patients with HRCT Score of 8 to <17/25(Group A) showed good prognosis & recovery with rapid decline in Oxygen requirements & improving Spo2 levels after initiation of Remdesivir. They had significantly lower duration of hospital stay (Mean stay of 10.4 + 2.1 days, $p < 0.05$) and significantly lower death rates (0%, $p < 0.05$) compared to Group B. Whereas covid -19 positive pregnant patients with high HRCT Score of >17/25 (Group B) did not respond even to prolonged Remdesivir therapy (10 days) and had significantly longer hospital stay (26 + 5.6 days, $p <0.05$) with significantly higher death rate (42.86% , $p<0.05$). Patients tolerated Remdesivir well without any side effects. Patients delivered healthy babies with no signs of respiratory illness or any untoward side effects on the baby due to use of Remdesivir.
Conclusion: Early referral of COVID -19 positive pregnant patient to hospital when lung lesions are still mild to moderate can be effectively treated with Remdesivir. But severe Covid -19 infection in pregnancy with rampant and excessive ground glass opacities on HRCT at the time of admission is difficult to treat and may not respond to Remdesivir therapy.

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1. Introduction

From its outbreak in late Dec 2019 in Wuhan China , novel coronavirus -19 infection has created havoc worldwide , not sparing even the pregnant women.[1,2] Until now the

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major studies - Adaptive Covid 19 Treatment Trial -1 (ACTT-1) by NIH[3] and the SIMPLE study by Gilead Sciences have shown promising results of Remdesivir in NONPREGNANT population but have excluded pregnant women. So there is a need to evaluate its effectiveness in pregnant women as well. Since our institute was transformed into a COVID CENTRE due to acute shortage of covid beds during the pandemic, we felt the need of the hour was also to cater to covid 19 positive PREGNANT patients.

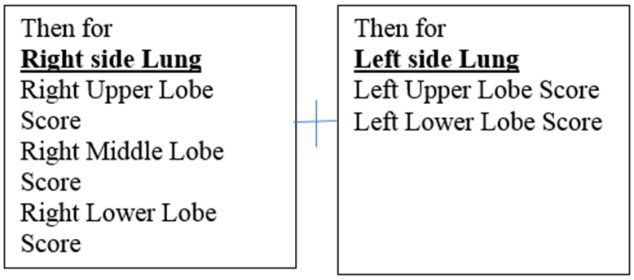
2. Materials and Methods

Design – Retrospective Observational Study

Total score (numerical)	Severity (category)
7 or less	Mild
8–17	Moderate
18 or more	Severe

N = In our study Covid 19 nasopharangeal swabs were performed on 73 of our antenatally registered near term pregnant patients, out of which 12 patients came positive. 81 confirmed covid positive pregnant patients were referred from outside for admission to our hospital at varied weeks of gestational age. Patients were divided in MILD, MODERATE & SEVERE CATEGORY depending on their HRCT scores on admission.[4] 25-point CT severity score by Chang et al. (devised for assessment of ARDS in patients with SARS in 2005) was used for this categorisation. Total sum of the individual 5 lobar scores indicates the overall severity.[4]

2.1. HRCT Severity Score



Gives Total HRCT Score out of 25.
0- Each lobe score = 0 - 5
1- No opacity
2- Upto 5% opacity
3- 5-25% opacity
4- 25-50% opacity
5- 50-75% opacity
6- More than 75% opacity.

Out of the 93 confirmed covid 19 positive pregnant patients, 15 patients were admitted to Intensive Care Unit(ICU) after physician consultation due to their disease severity and received Remdesivir therapy. Remaining 78 pateients were of MILD CATEGORY with HRCT score of 7 or less and did not require ICU admission and hence were excluded from receiving Remdesivir therapy.

These 15 patients were divided into 2 groups

Group A- (Moderate Category) including covid -19 positive pregnant patients with HRCT score of 8 to <17/25 had 8 patients.

Group B- (Severe Category) including covid -19 positive pregnant patients with high HRCT Score of >18/25 had 7 patients.

Enrollment = from March 2020 till June 2021

Analysis = Intention to treat

Primary Outcome = To assess clinical improvement of patient after 5 days of initiation of Remdesivir therapy in terms of

1. Oxygen requirement (litres/ min)
2. Spo2 levels (%)
3. Length of hospital stay (in days)
4. Death rate (%)
5. HRCT score on day 10 after initiation of remdesivir therapy(out of 25)

Secondary Outcome =

1. To assess side effects of Remdesivir therapy on the mother.
2. To assess effects of Remdesivir on the baby in utero during antenatal period and after delivery.

2.2. Summary of Remdesivir Action, Initiation Criteria, Dosage, Monitoring & Discontinuation criteria at our Institute

2.2.1. Mechanism of action of remdesivir

Remdesivir is the only FDA-approved prodrug for the treatment of COVID-19 patients. The active form of remdesivir forms an adenosine triphosphate analog that inhibits the viral RNA-dependent RNA polymerase (RdRp). Remdesivir resembles an RNA building block. Shortly after adding remdesivir, the enzyme RdRp stops being able to add more RNA subunits. This halts genome replication.

2.2.2. Initiation criteria

1. Age > 18 yrs.
2. Pregnancy at various weeks of gestational age.
3. Lab confirmed SARS CoV-2 Infection by RTPCR.
4. Evidence of lower respiratory tract infection at time of admission based on one of the following –

   (a) Radiographic Ground glass opacities and HRCT score ranging from > 8 / 25 & above.

      i. HRCT score from 8/25 upto 17/25 = Moderate disease.

ii. HRCT score >17/25 = Severe disease.

(b) Spo2 < 94% On Room air.

(c) Requiring Supplemental Oxygen or Mechanical Ventilation (BIPAP).

5. No limit to duration of symptoms before admission.

2.2.3. Exclusion criteria

1. Mild disease with HRCT score < 7/25
2. Spo2 > 94%.
3. Pt. who did not require ICU admission.

3. Dosage of Remdesivir Therapy

3.1. Standard therapy

200 mg of intravenous Remdesivir on day 1 followed by 100 mg of IV Remdesivir for the next 4 days.

3.2. Prolonged therapy

Continued administration of intravenous Remdesivir 100mg per day after standard therapy of 5 days for the next 5 days. Total duration of therapy for 10 days.

3.3. Monitoring during remdesivir therapy

1. Blood levels of Complete Blood Count(CBC), C-Reactive Protein(CRP), AST(SGOT), ALT(SGPT), Serum Creatinine, D- dimer, Serum LDH, were noted before initiation of therapy and on day 5 after initiation of therapy for monitoring of maternal side effects.
2. Ultrasound of fetus with Obstetric Doppler study was done at around 28-30 weeks of gestation to evaluate for any fetal abnormalities in terms of fetal growth, liquor and fetal blood supply. Regular weekly NON STRESS TEST (NST) was also done to evaluate fetal well being after 32 weeks of gestation. Also after delivery, baby was thoroughly evaluated by a paediatrician to note for any side effects on the baby.

3.4. Discontinuation criteria

1. AST & OR ALT > 5 times the upper limit of normal
2. Impaired eGFR <30 ml/ min or patient requiring hemodialysis or hemofiltrarion
3. Allergy to the drug

We have used the "Online Calculator soup" for calculating our results. The mean with confidence interval of 95% was calculated for variables like patients age in years, weeks of gestation, patients oxygen saturation for group A and group B. Also mean was calculated for clinical parameters like days of oxygen requirement & duration of hospital stay for patients in group A & group B. To determine differences between the group variables & to determine whether this difference is statistically significant or not, the Independent sample t tests and the Pearson chi squared tests were performed.

History of 8 confirmed covid positive pregnant patients with HRCT score 8 to <17/25 (GROUP A) is tabulated in table 1a. The mean age group is 30.37 + 4.45 years. The mean weeks of gestation of pregnancy was 32 weeks + 4.9 weeks. The most common presenting symptom was fever and cough. The mean Spo2 was 89.75 + 1.98%. The most common co- morbidity was pregnancy induced hypertension.

History of 7 confirmed covid positive pregnant patients with HRCT score >17/25 (Group B) is framed in table 1b. The mean age group is 30.42 + 5.12 years. The mean weeks of gestation of pregnancy was 30.1 weeks + 5.08 weeks. The most common presenting symptom was fever, cough and breathlessness. The mean Spo2 was 85.42 + 3.82%. The most common co- morbidity was pregnancy induced hypertension.

Clinical Parameters Of Group A pregnant patients are demonstrated in table 2a. The oxygen requirement rapidly decreased with initiation of remdesivir therapy. The mean duration of oxygen requirement was for 9.62+ 2.77 days. The mean duration of hospital stay was 11.62 + 3.37days. Death rate was 0% and the fetal outcome was good with no baby developing respiratory illness.

Clinical parameters of Group B covid positive pregnant patients with high HRCT score of >17/25 are demonstrated in table 2b. The oxygen requirement remained high and few patients also required non invasive ventilation (BIPAP) even after initiation of remdesivir therapy. The mean duration of oxygen requirement was for 19.14+ 2.26 days. The mean duration of hospital stay was 19.57 + 2.69 days. Death rate was 42.86% and the fetal outcome was good with no baby developing respiratory illness in the mothers who survived. The length of hospital stay and the death rate was significantly more in Group B compared to Group A.

4. Discussion

During this ongoing covid pandemic, its need of the hour to evaluate the effectiveness of drugs which may be helpful in its treatment. Remdesivir has shown promising results in clinical improvement in covid 19 patients, but it has not been evaluated in pregnant patients.[5] In our retrospective study, remdesivir therapy was associated with a significantly shorter time to clinical improvement. The mortality rate was lower in the remdesivir group, and the results too were statistically significant. The magnitude and direction of these associations were similar to those shown in ACTT-1.[6]

Our study included Covid -19 positive pregnant women than previous remdesivir clinical trials where pregnant women were totally excluded. Our results provide important evidence that remdesivir therapy is associated with decreased time to clinical improvement in covid -19 positive

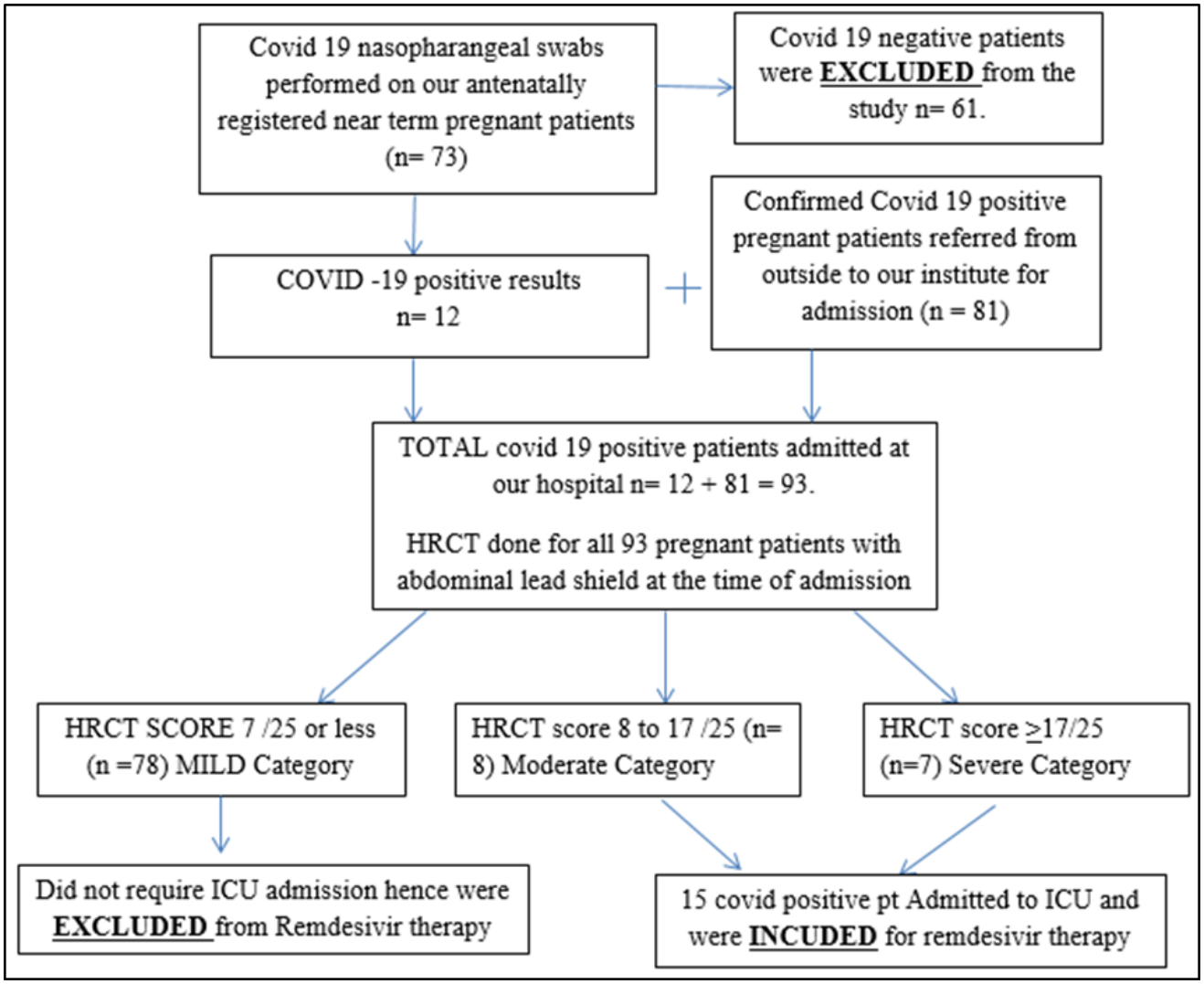


Fig. 1: Flow Chart demonstrating patient inclusionprocess

pregnant women.

In most of the studies in literature like by Beigel JH et al, the remdesivir group has received 5 days of therapy, which supports recommendations for an initial 5-day course for most patients. However in the study by Goldman JD et al, there was use of 10 day treatment and the comparison of 5 days vs 10 days showed similar efficacy.[7] Also the study by Spinner CD at al showed that 5 days course, but not a 10-day course, was associated with a significant improvement in disease severity.[8] As per the study by Kapczynski et al.[9] our finding that a 5-day treatment course was associated with a clinical benefit is important, due to global shortages of remdesivir and the potential for even greater supply constraints moving forward .Hence it is advisable to wisely use the present available remdesivir resources.

In our study there was no death in the Covid -19 positive pregnant patients with moderate disease who received remdesivir early, corresponding with the RECOVERY TRIAL conducted by Horby P et al.[10] The results of our study also co-relates with the ACTT-4 trial where patients breathing ambient air or nasal cannula oxygen benefitted more from treatment with remdesivir, whereas patients receiving higher levels of respiratory support, such as mechanical ventilation, did not benefit.[11] This emphasises the fact that early initiation of remdesivir therapy when patient is mildly breathless with less oxygen requirement and better oxygen saturation, will have better clinical outcome compared to those COVID positive pregnant patients who present late and have more severe symptoms. Hence its co-relation with HRCT score is important. patients with low HRCT Score respond better to remdesivir herapy compared to tose with high HRCT Score. There are other ongoing trials like ACTT -4 to study the effectiveness of remdesivir combined with dexamethasone on one arm and

remdesivir in combination with baricitinib on the other.[11] Their results are still awaited and will be a guide to future treatment protocols.

5. Conclusions

This study suggests that remdesivir was associated with a significant decrease in the time to clinical recovery among Covid 19 positive pregnant patients admitted early to the hospital with low HRCT Score .for treatment of COVID-19. These results provide further evidence that remdesivir is effective in reducing the duration of COVID-19 illness, that a 5-day treatment course may be sufficient, and that patients with mild and moderate disease likely benefit most. The high mortality in severely affected group inspite of receiving remdesivir suggests that late onset of remdesivir when the disease has already progressed as suggested by high HRCT Score is of less or no benefit. Thus early use of remdesivir when symptoms are mild to moderate is effective and beneficial in reducing hospital stay and Covid-19 related morbidity and mortality.

6. Conflict of Interest

The author declares no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

7. Source of Funding

None.

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