INTRODUCTION

The novel coronavirus disease (COVID-19) emerged in December 2019 and rapidly became a pandemic. Globally, as of now, 203,178,675 people are infected, including four million deaths. This led to the search of desperate public health measures including the quest for effective treatments. Despite the fact that a number of therapeutic agents have been tested for the treatment of Covid-19, no antiviral drug has proved to be efficacious. Experts from the World Health Organization initiated mortality trials comparing four drugs including Remdesivir, Hydroxychloroquine, Lopinavir, and interferon beta-1a. The rate of mortality, initiation of ventilation, and length of hospital stay were not definitely reduced by any of the trial drug.
One of the many promising candidates for this purpose was Remdesivir, which is a drug with effective antiviral properties. Remdesivir has a broad spectrum of activity and acts by inhibiting RNA-dependent RNA polymerases (RdRp) and subsequently causes arrest in RNA synthesis. It has been used to treat Filo viruses, Corona viruses, paramyxoviruses and pneumoviridae. In Wuhan, China the first randomized, placebo-controlled trial of Remdesivir among patients with COVID-19 was begun. Unfortunately, they were unable to access the efficacy of Remdesivir as the trial was unable to successfully complete recruitment. However, results from a large randomized, double-blind clinical trial showed that a 10-day Remdesivir course had significantly faster recovery time (11 days) in COVID-19 patients when compared to those who received placebo (15 days). Contradicting this evidence, the WHO led SOLIDARITY trial in over 40 countries worldwide showed no benefit of Remdesivir on mortality or length of hospital stay. Despite such conflicting results, on 1st May 2020, Remdesivir was granted Emergency Use Authorization by the US Food and Drug Administration for the treatment of patients with severe COVID-19. Later this was expanded to include non-severe patients. Final approval was given on the basis of three Randomized controlled trials which showed benefit of Remdesivir over placebo in reducing mortality. Hundred and Eight clinical trials of Remdesivir for COVID-19 are currently registered with U.S National Library of Medicine. The only contraindications to the use of Remdesivir were pre-existing hepatic dysfunction as manifested by Alanine Aminotransferase (ALT) levels more than 5 times the upper limit of normal and reduced Glomerular filtration rate (<60 ml/min). Hence, those COVID-19 severe disease patients who received Remdesivir were analyzed in Rem group while those who could not receive Remdesivir due to unavailability or contra-indications were analyzed in Non-Rem group. Those patients who did not receive Remdesivir due to unavailability of the drug in the early days or any contraindication to its use were used as a comparison group for the purpose of this analysis. We recorded patient’s demographics, clinical details and laboratory parameters at admission. The main outcome of interest was in-hospital mortality. All data was entered on a REDCap database and Stata version 14 was used for analysis. Mean (SD) were reported for continuous data after checking normality. Median (IQR) was used for non-normally distributed data. Categorical variables were reported as numbers and percentages. Either Student’s t-test or Mann Whitney U test were used to compare continuous data. Chi square or Fischer’s Exact test was used to compare categorical data. P-value ≤ 0.05 was considered significant.

RESULTS

A total of 268 patients were enrolled in the study. Remdesivir was given to 102 patients while 166 were in the non-Remdesivir group. The
baseline characteristics of both Remdesivir and non-Remdesivir groups are shown in Table-I.

Overall more than three fourth (76.5%) of the patients were male and there was no difference in gender or age distribution of the two groups. Distribution of major comorbid conditions like diabetes mellitus, hypertension and heart disease was not different between the two groups. Most patients presented with fever, cough and shortness of breath as presenting symptoms in both groups (p>0.05). Among the physical parameters in emergency room, median peripheral oxygen saturation (SpO2) was significantly lower in the Remdesivir group (86% vs 88%; p=0.032). Similarly, the median PaO2/Fio2 ratio was much lower for the Remdesivir group (115; IQR=72.9-242.5) at presentation compared to the non-Remdesivir group (187; IQR=104-268) (p=0.032). In the Remdesivir group, 40% patients had severe ARDS while in the non-Remdesivir group only 19% had severe ARDS (p=0.002). Patients with clinical severity of moderate, severe and critical were included in the study as those with less than moderate disease were not admitted to hospital for management. Remdesivir group had more patients (92%) with combined severe disease and critical disease while the non-Remdesivir group had a majority of patients with critical disease (80%) (p-value=0.001). Need for high flow oxygen at least 5 L was more in the Remdesivir group (81% vs 50.6%; p=0.000). However, both the groups had similar need for invasive ventilation and non-invasive ventilation (p>0.05). Median SOFA score was much higher in non-Remdesivir group depicting multiorgan dysfunction compared to the Remdesivir group (5 vs 2; p=0.000).

There were no major differences in baseline laboratory parameters (Table-II), however, inflammatory markers like Ferritin and IL-6 were markedly raised in the non-Remdesivir group compared to Remdesivir group (p<0.05). Median D-dimer was 0.6 ng/ml in Remdesivir group while 1.8 ng/ml in the non-Remdesivir group (p=0.000). Pro-calcitonin was significantly higher in the non-Remdesivir group (p=0.013). Chest X-ray findings were scored using RALE scoring and the median RALE score was 6 (IQR=5-8) in Remdesivir group while 5 (IQR=4-7) in the non Remdesivir group (p value 0.002).

When mortality was compared between the two groups (Table-III), no major difference in hospital mortality was observed (46% in

### Table-I: Characteristics of COVID-19 patients admitted at The Indus Hospital-Korangi Campus.

| Variable               | Remdesivir n=102 | Non-Remdesivir n=166 | p-value |
|------------------------|------------------|----------------------|---------|
| **Age**                | 55.0 ± 12.8      | 56.2 ± 13.3          | 0.485   |
| **Gender**             |                  |                      |         |
| Male                   | 75 (73.5)        | 130 (78.3)           | 0.370   |
| Female                 | 27 (26.5)        | 36 (21.7)            |         |
| **Hypertension**       |                  |                      |         |
| Yes                    | 47 (46.1)        | 72 (43.4)            | 0.665   |
| No                     | 55 (53.9)        | 94 (56.6)            |         |
| **Diabetes**           |                  |                      |         |
| Yes                    | 52 (51.0)        | 74 (44.6)            | 0.308   |
| No                     | 50 (49.0)        | 92 (55.4)            |         |
| **Heart Disease**      |                  |                      |         |
| Yes                    | 11 (10.8)        | 17 (10.2)            | 0.888   |
| No                     | 91 (89.2)        | 149 (89.8)           |         |
| **Fever**              |                  |                      |         |
| Yes                    | 86 (84.3)        | 139 (83.7)           | 0.900   |
| No                     | 16 (15.7)        | 27 (16.3)            |         |
| **Cough**              |                  |                      |         |
| Yes                    | 51 (50.0)        | 101 (60.8)           | 0.089   |
| No                     | 51 (50.0)        | 65 (39.2)            |         |
| **Shortness of breath**|                  |                      |         |
| Yes                    | 76 (74.5)        | 139 (83.7)           | 0.066   |
| No                     | 26 (25.5)        | 27 (16.3)            |         |
| **Systolic BP**        | 138 (118-151)    | 139 (123-153)        | 0.437   |
| **Diastolic BP**       | 80 (71-80)       | 80 (72-90.5)         | 0.847   |
| **Pulse**              | 100 (86-110.5)   | 106 (92-117.5)       | 0.233   |
| **Respiratory Rate**   | 32 (26-38)       | 30 (24-36)           | 0.147   |
| **Oxygen Saturation**  | 86 (78-90)       | 88 (76-93)           | 0.032   |
| **SOFA Score**         | 2 (2-3.5)        | 5 (4-8)              | <0.0001 **|
| **PaO2/FiO2 Ratio**    | 115              | 187.5                | 0.032   |
|                        | (72.9-242.5)     | (104.3-268.3)        |         |
| **Clinical Severity**  |                  |                      |         |
| Moderate               | 8 (7.8)          | 18 (10.8)            | 0.001 **|
| Severe                 | 27 (26.5)        | 15 (9.0)             |         |
| Critical               | 67 (65.7)        | 133 (80.1)           |         |
| **Invasive ventilation**|                |                      |         |
| Yes                    | 37 (36.3)        | 66 (39.8)            | 0.569   |
| No                     | 65 (63.7)        | 100 (60.2)           |         |
| **ARDS**               |                  |                      |         |
| Severe ARDS            | 41 (40.2)        | 30 (19.2)            | 0.002   |
| Moderate ARDS          | 20 (19.6)        | 52 (33.3)            |         |
| Mild ARDS              | 24 (23.5)        | 46 (29.5)            |         |
| Not Present            | 17 (16.7)        | 28 (17.9)            |         |
| **Oxygen Requirement** |                  |                      |         |
| ≥5 Litres              | 83 (81.4)        | 84 (50.6)            | <0.0001 **|
| < 5 Litres             | 19 (18.6)        | 82 (49.4)            |         |
| **Non Invasive Ventilation**|          |                      |         |
| Yes                    | 39 (38.2)        | 63 (38.0)            | 0.963   |
| No                     | 63 (61.8)        | 103 (62.0)           |         |

^Median (IQR), βMean (SD), P value <0.05, **<0.001
Remdesivir group vs 40.4% in non-Remdesivir group; (p=0.46). Median length of hospital stay was 12 (IQR=7.5-14.5) days compared to 10 days (IQR=6-14) in non-Remdesivir group (p=0.009).

With regards to adjunctive therapies, (Table-IV) there was no significant difference in the use of Tocilizumab between the two groups (p>0.05). Use of antibiotics was higher in non-Remdesivir group (p=0.000) while use of methyl prednisolone was higher in Remdesivir group (p=0.001). Similarly, the use of therapeutic anticoagulation was significantly higher in the non-Remdesivir group compared to Remdesivir group (p=0.001).

The median number of doses used for this cohort was 5 (IQR=2-5), which corresponds to 600mg Remdesivir per patient. The median duration of

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**Table-III: Outcome COVID_19 patients by use of Remdesivir.**

| In-hospital complications | Remdesivir | Non-Remdesivir | p-value |
|--------------------------|------------|----------------|---------|
| None                     | 36(38.3)   | 78(50.0)       |         |
| Cardiac Abnormalities    | 22(23.4)   | 27(17.3)       |         |
| Nosocomial Infection     | 16(17.0)   | 30(19.2)       |         |
| CNS Abnormalities        | 3(3.2)     | 5(3.2)         |         |
| Septic Shock             | 6(6.4)     | 32(20.5)       | <0.0001**|
| MODS                     | 15(16.0)   | 23(14.7)       |         |
| AKI                      | 10(10.6)   | 46(29.5)       |         |
| Thromboembolism          | 0          | 7(4.5)         |         |
| Barotrauma               | 0          | 4(2.6)         |         |
| DIC                      | 1(1.1)     | 9(5.8)         |         |
| Length of hospital stay  | 12(7.5-14.5) | 10(6-14)     | 0.009* |
| Mortality                |            |                |         |
| Alive                    | 55(53.9)   | 99(59.6)       | 0.406   |
| Dead                     | 47(46.0)   | 67(40.4)       |         |

^Median (IQR), *does not add up to 100, P value *<0.05, **<0.001.
symptoms at which the Remdesivir was administered was 10 days (IQR=8-11). The maximum Alanine amino transferase after administration of Remdesivir was 81 (IQR=42-136) while maximum creatinine was 1.1 (0.9-2.2) in our patients.

**DISCUSSION**

We believe this is the first report of the use of Remdesivir from our country. Randomized Clinical Trials have shown some benefit of Remdesivir in COVID-19 pneumonia. However, our data is from the first wave of COVID-19, when practitioners did not have much idea regarding the optimum dosing and duration of therapy as well as expected side effects of this uncommon drug. With more data emerging on the management of COVID-19, it is now evident that Remdesivir is one of the mainstay therapies for halting the progression of COVID-19 pneumonia.

Although our data shows no effect of Remdesivir on mortality, we have only been able to look at in-hospital mortality while a recent meta-analysis published in January 2021 suggests that 28 day mortality and oxygen support through 14-28 days is affected by the use of Remdesivir. Hence, it is quite possible that our groups would have shown a difference if they were followed for a longer period of time. Secondly, our treatment groups were not balanced to begin with. The Remdesivir group was characterized by marked hypoxia and features of ARDS due to COVID-19 pneumonia allowing easy decision making for using the drug. On the other hand, the non-Remdesivir group seems to be more severely sick as indicated by higher median SOFA scores and high pro-calcitonin suggesting the onset of multi organ dysfunction and possible secondary bacterial infection complicating their outcomes and prognosis. The use of Remdesivir was abandoned in this group due to presence of multi organ dysfunction and probable liver and renal injury contraindicating the use of Remdesivir. However, the overall mortality reported from another one of our recently published papers from this cohort was 39% which was not very different from the Remdesivir group here.

One important difference to highlight in our data is that Remdesivir was being administered to people at a median 10th day (IQR=8-11) of illness during the first wave of COVID-19. Later, published data indicated that this was probably already late. Hence, guidelines adapted the 10 day rule and now it is understood that Remdesivir benefit is maximized by giving it in hypoxic patients within 10 days of illness. In fact, some data suggests the use of Remdesivir in non-hypoxic patients earlier in the course of the disease if there is evidence of COVID-19 pneumonia. We did not identify any major side effects of Remdesivir in our patients. Maximum ALT and serum creatinine were not significantly raised.

Our study has a number of limitations including non-random treatment allocation leading
to selection bias. Co-administration of other compassionate therapies like antibiotics, steroids and anticoagulation (both prophylactic as well as therapeutic doses) could also confound the results. These effects are not easy to tease out because of the observational nature of the study. An interesting observation was that most patients in the non-Remdesivir group were given antibiotics, had higher pro-calcitonin levels and higher SOFA scores indicating the onset of secondary bacterial infection or an already complicated clinical course with multi-organ failure. Hence this group, was never a candidate for Remdesivir therapy. While most patients in the Remdesivir group had pure hypoxia, need for high flow oxygen and severe ARDS without evidence of multi-organ failure as evidence by a lower SOFA score. Even in this group, we see a high mortality and no benefit of Remdesivir in our patients. We believe this group of patients were too late in multiple studies, hence we were not able to define the effectiveness of the drug early in the course of the disease. Hence, the search for better therapeutic modalities and optimum timing of therapy is important in management of COVID-19 patients.

**Conclusion:** Remdesivir did not show any mortality benefit among severe COVID-19 patients in our data. Randomized controlled trials are needed to define the effectiveness of the drug early in the course of the disease.

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**Authors Contributions:**

QS: Conceived, designed, data collection, data analysis, manuscript writing.
SS: Conceived, designed, data collection, manuscript review.
AR: Designed, data collection, data analysis, results writing.
MH, RS & SS: Designed, data collection, manuscript review.