

Association of remdesivir with poor clinical outcomes in Covid-19

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Abstract

Introduction: Need of an antiviral against Covid-19 prompted clinical trials all over the world and based on initial promising trends, remdesivir was widely used all over the world, including India (compassionate use). Subsequent trials have been conflicting in their results and the utility of the drug has been widely debated.

Methods: This is a record-based retrospective cohort study carried out in a 1000-bedded government teaching hospital in North India. The medical e-records of the Covid-19 positive patients who were admitted between June and November 2020 were reviewed for eligibility. After making the necessary exclusions, 112 patients were included in the remdesivir cohort and 85 in the standard care cohort. All the baseline characteristics of relevance and details of hospital admission were collected. The following outcomes in relation to remdesivir administration were assessed: all-cause mortality until discharge – stratified as per baseline oxygen support, age, gender and comorbidities; proportion of severe and non-severe patients progressing to mechanical ventilation later on; and time to clinical recovery in survivors.

Results: There was a statistically significant association of higher mortality with the administration of remdesivir (odds ratio, OR 2.3, p-value 0.008) with a Cox regression hazard ratio of 1.590 (CI 0.944–2.679). The trend towards poorer outcomes in the remdesivir cohort persisted even after sub-stratification for age, gender, baseline severity (oxygen need) and comorbidities but failed to reach statistical significance in most of the strata. Similarly, remdesivir administration was associated with higher rates of progression to mechanical ventilation amongst those severe and non-severe patients who were not on mechanical ventilation at admission (49 % versus 15 %, p-value < 0.001, OR 5.2). This association was significant overall as well as for severe category patients when assessed separately (56% versus 26 %, p-value 0.04, OR 3.1). There was, however, no difference in the days taken for clinical recovery between the two groups (13.23 days versus 12.8 days, p-value 0.77).

Conclusion: Remdesivir administration was associated with overall worse clinical outcomes. This study contradicts the benefits shown with remdesivir in previous clinical trials done in controlled settings and highlights the challenges that newer therapies face in real life hospital settings. There is a need to include diverse ethnic groups in the future clinical trials of the drug if to be used.

Introduction

Remdesivir (also known as GS-5734) is a prodrug that was first developed against the Ebola virus in 2017 and was identified as a potential therapy for the SARS-CoV 2 based on in-vitro studies as well as in primate models (1–5). This prompted clinical trials all over the world and based on the early results, the FDA issued emergency use authorization to remdesivir on 1 May 2020 (6).

The earliest randomised controlled trial (RCT) of remdesivir in Covid-19 was conducted in China and showed numerical tendencies favouring treatment with remdesivir (7). The phase 3 Adaptive Covid-19 Treatment Trial-1 (ACTT-1) demonstrated a shorter time to clinical recovery in the remdesivir arm, for

those on supplemental oxygen (8). However, the largest RCT of remdesivir till date, the WHO sponsored solidarity trial did not find any reduction in overall mortality, need of ventilation or the duration of hospital stay (9). Not surprisingly, there is no consensus amongst the leading health organisations of the world regarding the use of remdesivir. Nevertheless, the drug was widely prescribed all over the world (compassionate use) during the pandemic, including in India. For more rational use of remdesivir, further detailed studies are the need of the hour.

In this study, we have retrospectively compared the outcomes of the patients who were administered remdesivir (out of trial, real world practices) with those receiving standard treatment alone in a tertiary care hospital in North India.

Methods

Study design and setting

The study was carried out at a 1000-bedded teaching hospital which is a tertiary level referral centre in the north Indian state of Uttarakhand. The institutional ethics committee, AIIMS, Rishikesh approved the study (No. 218/IEC/IM/NF/2020). The data collection was done through the e-medical records on the National Informatics Centre's e-hospital portal being used by the hospital.

Study population and patient selection

All Covid-19 positive adult patients admitted between June and November, 2020 were reviewed for eligibility. Covid-19 positivity was defined as having confirmed reverse transcriptase polymerase chain reaction (RT-PCR) positivity for SARS-Cov-2 on nasopharyngeal swab; or clinical features and chest radiological findings highly suggestive of Covid-19 infection with no other explainable diagnosis.

All those who were administered remdesivir within a trial were excluded. We also excluded all those participants who had received any other experimental therapy apart from remdesivir, or those who had refused to give consent for use of their medical data for research purposes at the time of hospital admission. A retrospective analysis of the eligible patients' medical records was carried out in which all the relevant patient parameters were collected and the patients were classified as per the WHO severity categories (10). All the study participants were divided amongst the two cohorts – remdesivir or standard care. Standard care comprised of isolation, hydration, nutrition, supportive pharmacotherapy as indicated (antipyretics, antiallergics, cough suppressants, antibiotics for other associated infections), treatment of comorbidities and oxygen/ ventilatory support, inotropes and renal replacement as and when indicated. Those in the remdesivir cohort received remdesivir as well as standard care whereas the latter cohort comprised of those who received standard care alone.

Study variables and outcomes

We collected all the baseline characteristics of relevance including demographics, symptoms, duration of illness, pre-existing co-morbidities, and medications. From the hospital course, data was collected for the

treatment given including oxygen interface, steroids, antimicrobials and supportive care needed. The baseline and follow up laboratory parameters were also noted. Duration of hospital stay (in days) was noted as well as the duration to clinical recovery from hospitalisation in survivors. Oxygen support was categorised into five strata for the ease of analysis, namely room air, low flow, high flow, non-invasive ventilation and invasive mechanical ventilation. 'Low flow' oxygen systems include nasal cannula, Hudson face mask and non-rebreather face mask (in non-tachypneic patients) whereas non-rebreather face masks in normopneic patients and high flow nasal cannula were included in 'high flow' systems (11).

The following outcomes were assessed:

1. All-cause mortality until discharge – stratified as per baseline oxygen support, age, gender and comorbidities.
2. Proportion of severe and non-severe patients progressing to mechanical ventilation later on.
3. Time to clinical recovery in survivors.

Statistical Analysis

Quantitative variables were compared using the Independent t-test (as the data sets were normally distributed) between two groups. For >2 groups, analysis of variance (ANOVA) was used. Qualitative variables were correlated using the Chi-Square test. Fisher exact was used when the expected frequency in any of the cell was <5. Relationships were assessed using Pearson or Spearman tests depending upon distribution. Multivariate regression (logistic for categorical and linear for continuous dependent variables) was used to determine the significant predictor variables.

We also did a survival analysis, following up patients from the date of symptom onset to death. We compared the time to death by treatment cohorts using unweighted Kaplan-Meier curves and univariate and multivariate Cox regression analysis. The effect of treatment was studied using an unadjusted and adjusted hazard ratio (HR) with 95% CI.

A p-value of <0.05 was considered statistically significant. The data was entered in the Microsoft EXCEL spreadsheet, and analysis was done using IBM Statistical Package for Social Sciences (SPSS) version 26.0 (Chicago, US).

Results

Of the 520 patients assessed for eligibility, 45 patients were excluded as they had missing consent forms and 125 were already enrolled in a clinical trial. Of the remaining 350, 145 were excluded because they received at least one of the other experimental therapies for Covid-19 (favipiravir, tocilizumab, interferon, ivermectin, hydroxychloroquine, lopinavir – ritonavir, or convalescent plasma). Data collection was started for 205 patients but eight were excluded subsequently as they had majority of variables missing. A total of 197 patients were included in the final analysis after all the necessary exclusions (Figure 1).

Of these, 146 (74 %) participants were males and 51 (26 %) were females. 112 (57 %) patients received remdesivir during the course of hospital stay whereas 85 (43 %) patients received standard care alone. In the remdesivir group, the mean age was 55.8 years and 86 (77 %) were males as compared to the mean age of 51 years and male population of 60 (71 %) in the standard care cohort. The proportion of non-severe, severe and critical patients was 17 %, 50 % and 33 % respectively in the remdesivir group versus 44 %, 33 % and 23 % respectively in the non-remdesivir cohort. The most common comorbidity in both the groups was hypertension followed by diabetes mellitus followed by chronic cardiac disease. Only 38 (34%) patients didn't have any comorbidity in the remdesivir group compared to 41 (48 %) in the non-remdesivir group. Overall, the participants in the remdesivir cohort had statistically significant higher baseline severity, age and comorbidities (hypertension and diabetes mellitus) (Table 1).

106 (95 %) of the 112 study participants received the 5-day course of therapy and six participants received the 10-day course of therapy. For the ease of categorisation, we have rounded off the duration for those who could not complete the course. 88 (79 %) of the patients were started on remdesivir within the first 10 days after symptom onset, whereas 23 were started at > 10 days (onset of symptoms could not be ascertained for one patient). Majority of patients in both the cohorts received steroids. A few patients also received high dose steroids as 'pulse' steroids (dexamethasone 40mg OD or methylprednisolone 250-500mg OD for 3-5 days and then tapered) when suspected to have rapid deterioration due to 'cytokine storm'. A statistically significant higher number of patients (109; 97%) received steroids in the remdesivir cohort (including 13 participants who received a pulse dose of steroid) compared to 75 patients (88%) in the standard care cohort (of which 8 received pulse dose too).

We found statistically significant higher odds of mortality with remdesivir compared to standard care alone ($p=0.008$, Odds Ratio, OR=2.3). However, the two groups varied significantly in terms of the baseline disease severity of the participants with the proportion of non-severe category patients being much higher in the non-remdesivir group. After doing indirect standardisation for baseline severity, the standardised mortality rate in the remdesivir cohort was 1.24 (much less than the OR, but was still higher for the remdesivir cohort). We also assessed the association of mortality with remdesivir administration after sub stratification for age, gender, comorbidities and baseline oxygen support. Only three comorbidities (diabetes mellitus, hypertension and chronic cardiac disease) were present in a significant number of patients and hence, only these were included in the final analysis. At least one of the three comorbidities was present in 74 (66%) remdesivir and 44 (52 %) non-remdesivir participants. There was a definitive trend towards association of mortality with remdesivir administration across all the sub-groups, with statistical significance reached for the elderly, females, hypertensives and those without chronic cardiac disease. Similarly, remdesivir administration was associated with higher rates of progression to mechanical ventilation amongst those severe and non-severe patients who were not on mechanical ventilation at admission. This association was significant overall as well as for severe category patients when assessed separately. There was, however, no difference in the days taken for clinical recovery between the two groups.

A Kaplan Meier curve was constructed comparing the duration of hospital stay with events as mortality and estimated the cumulative probability of death, compared in between the two cohorts. There is an increased cumulative mortality in the remdesivir cohort (Figure 2). Patients treated with remdesivir had a higher Cox regression hazard ratio suggestive of a trend towards higher mortality (HR 1.590, 95 % CI 0.944-2.679, p-value 0.081).

Discussion

In this retrospective analysis of medical records, we found a statistically significant association of mortality with the administration of remdesivir when compared with the standard treatment alone (43 % versus 25 %, p value=0.008, Odds ratio = 2.3). The Kaplan Meier curve also showed more hazard events (death) when compared with standard care curve (Figure 2). As the baseline clinical severity of the two cohorts was not matched, we stratified the population as per the oxygen support required at admission. We didn't find any statistically significant difference in mortality in any of the groups after stratification for the baseline oxygen support. This is consistent with the previous studies by Wang et al and trials like Solidarity and ACTT-1 (7–9). However, while our study showed a trend towards higher mortality in the remdesivir cohort, the ACTT-1 showed a trend towards lower mortality with the most significant reduction in those receiving oxygen support (without any mechanical ventilation) (8). The severity adjusted Standardised Mortality Rate was 1.24 times higher in the remdesivir group (which is close to one and much less than the crude odds ratio of 2.3). Our study also showed a trend towards higher mortality with remdesivir after stratification by age, gender and underlying comorbidities.

We also assessed the progression of patients to mechanical ventilation in non-severe and severe category patients (those who were not on mechanical ventilation at admission). There was a statistically significant association with lower rates of progression to mechanical

ventilation in the non-remdesivir group (49 % vs 15 %; p-value <0.001). This finding is opposite to that seen in the Solidarity trial and meta-analyses by Kaka et al and Vegivinti et al (12,13). As stated above, the proportion of non-severe patients was higher in the non-remdesivir cohort of our study when compared with the remdesivir cohort. When we did subgroup analysis of progression to mechanical ventilation separately with only the non-severe and only the severe patients, there was no statistically significant difference (p-value 0.06) in the non-severe group but was still significant for the severe group patients (p-value 0.04).

In those patients who survived till 28 days/ hospital discharge (whichever was longer), we assessed the days to clinical recovery which was only slightly higher for remdesivir cohort when compared to standard care (13.2 days vs 12.8 days) but failed to reach clinical significance (p-value = 0.77). These findings are consistent with the Solidarity trial, whereas ACTT-1 and Wang et al. reported a reduction in the time to clinical recovery with remdesivir(7–9). While the study by Wang et al was limited by its small sample size, the ACTT-1 trial had excluded patients who were expected to be discharged within 72 hours. Hence, it is difficult to extrapolate the results of the ACTT-1 in routine practice, as has been pointed out by many

researchers (14). A large retrospective cohort study done on 2344 US veterans showed that the duration of hospital stay was significantly higher for the remdesivir cohort (3 days vs 6 days) when compared with matched controls (15). For a drug that has no mortality benefit, prolonged hospital stays would mean wastage of the precious hospital beds during the pandemic. The most likely explanation is that the clinicians may have not discharged the patients even after clinical improvement just in order to complete the course of remdesivir.

The explanation for the poor outcomes seen with remdesivir may lie in the retrospective nature of our study. As stated, we have only included those participants who were administered remdesivir outside of any clinical trial (compassionate use) and it is reasonable to assume that an experimental drug would only be used by the treating physician in the setting of worsening clinical condition, especially when the supply is scarce and the drug is expensive. Although we did stratify the patients as per the baseline oxygen support, but the true clinical condition is dictated by much more than merely the oxygen support and depends on a large number of clinical parameters. Hence it is reasonable to assume that the results may be affected by the unadjusted confounders, as in all observational studies.

Limitations

Our study had a number of limitations. Firstly, the sample size was small and uneven in both the cohorts, leaving little scope for meaningful stratification. Many observations were made and trends noted in our present study that would have required larger sample sizes to reach statistical significance. Secondly, ours was a retrospective study and the two cohorts were not matched for baseline characteristics. Thirdly, many parameters like respiratory rate, precise fraction of inspired O₂ (FiO₂), patient position, follow up investigations and adverse drug reactions, etc were not documented in our case records and hence, these could not be included in the analysis. Lastly, there was no follow up of patients.

To conclude, the present study is a retrospective analysis of medical records of patients from real-life hospital settings in the midst of a pandemic in a developing nation. The study highlights the challenges that newer therapies face in real life hospital settings. Remdesivir had emerged as a promising tool against Covid-19 in the studies done in the developed countries (ACTT-1), but was found to make no difference to outcomes in a more global trial (the Solidarity trial). Despite its limitations, the results of this study should guide us to conduct more RCTs in developing nations and involving different ethnic groups to ascertain the role of novel drugs in the treatment of Covid-19. It also highlights that the results of a clinical trial (controlled setting) may not be entirely reproducible in a real-life setting.

Declarations

Contributors

RL, DA and Arjun contributed to the data collection, their analysis and was involved in manuscript writing. PKP, YAB and GC gave the concept, interpreted analysis, critically reviewed the draft, and approved it for publication along with all authors.

Data sharing

It will be made available to others as required upon requesting the corresponding author.

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Conflicts of interest

We declare that we have no conflicts of interest.

Funding source

None

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Tables

Table 1: Baseline characteristics of remdesivir and standard care cohorts				
Baseline Characteristic		Remdesivir (N = 112)	Standard care (N = 85)	P-value
Age (years)	Mean, Median and Mode	55.8, 58 and 57	51, 51, 57	0.02
	Standard Deviation	14.5	15.5	
	Minimum and Maximum	25 and 85	18 and 81	
	≥65 years	31 (27.6 %)	19 (22.4 %)	0.40
	<65 years	81 (72.4 %)	66 (77.6 %)	
Gender	Males	86 (77 %)	60 (71 %)	0.33
	Females	26 (23 %)	25 (29 %)	
Pre-existing comorbidities	Chronic cardiac disease (not hypertension)	21 (19 %)	14 (16.5 %)	0.68
	Hypertension	53 (47 %)	25 (29 %)	0.01
	Diabetes Mellitus	50 (45 %)	23 (27 %)	0.01
	With no co-morbidity	38 (34 %)	41 (48 %)	0.04
Oxygen support at hospitalisation	Room Air	19 (17 %)	30 (35 %)	0.001
	Low flow Oxygen support	32 (28.6 %)	28 (33 %)	
	High flow oxygen support	34 (30 %)	8 (9.4 %)	
	Non-invasive ventilation	19 (17 %)	12 (14 %)	
	Invasive mechanical ventilation	8 (7 %)	7 (8.2 %)	
Covid-19 Severity at Baseline	Non-severe	19 (17 %)	37 (44 %)	<0.001
	Severe	56 (50 %)	28 (33 %)	

	Critical	37 (33 %)	20 (23 %)	
Receipt of steroids during hospitalisation	Any dose	109 (97 %)	75 (88 %)	0.01
	Pulse steroid	13 (12 %)	8 (9 %)	0.62

Table 2: Various outcomes of remdesivir and standard care cohorts

Outcome		Remdesivir cohort	Standard care cohort	p-value	Odds Ratio
All-cause mortality	Overall	48 (43 %)	21 (25 %)	0.008	2.3
	Age stratified				
	≥ 65 years	19 (61 %)	5 (26 %)	0.02	4.4
	<65 years	29 (36 %)	16 (24 %)	0.13	
	Gender stratified				
	Males	33 (38 %)	14 (23 %)	0.06	
	Females	15 (58 %)	7 (28 %)	0.03	3.5
	Stratified as per underlying comorbidity				
	Diabetics	25 (50 %)	6 (26 %)	0.06	
	Non-diabetics	23 (37 %)	15 (24 %)	0.12	
	Hypertensives	31 (58 %)	8 (32 %)	0.03	3
	Non-hypertensives	17 (29 %)	13 (22 %)	0.37	
	Cardiac diseased	6 (29 %)	4 (26 %)	1*	
	Non-cardiac diseased	42 (46 %)	17 (24 %)	0.004	2.7
	Stratified as per oxygen support at admission				
	Room air	4 (21 %)	1 (3 %)	0.13*	
	Low flow oxygen	12 (38 %)	5 (18 %)	0.09	
	High flow oxygen	17 (50 %)	3 (38 %)	0.8*	
	Non-invasive ventilation	10 (53 %)	5 (42 %)	0.55	
	Invasive mechanical ventilation	5 (62 %)	7 (100 %)	0.25	

Progression to mechanical ventilation in those not requiring mechanical ventilation at admission	Overall	35 (49 %)	10 (15 %)	< 0.001	5.2
	Non-severe category only	5 (28 %)	2 (5 %)	0.06*	
	Severe category only	30 (56 %)	8 (26 %)	0.04	3.1
Days to clinical recovery in survivors		13.23 ± 6.5 (n = 62)	12.8 ± 9.8 (n = 64)	0.77	

*Fisher exact used.

Figures

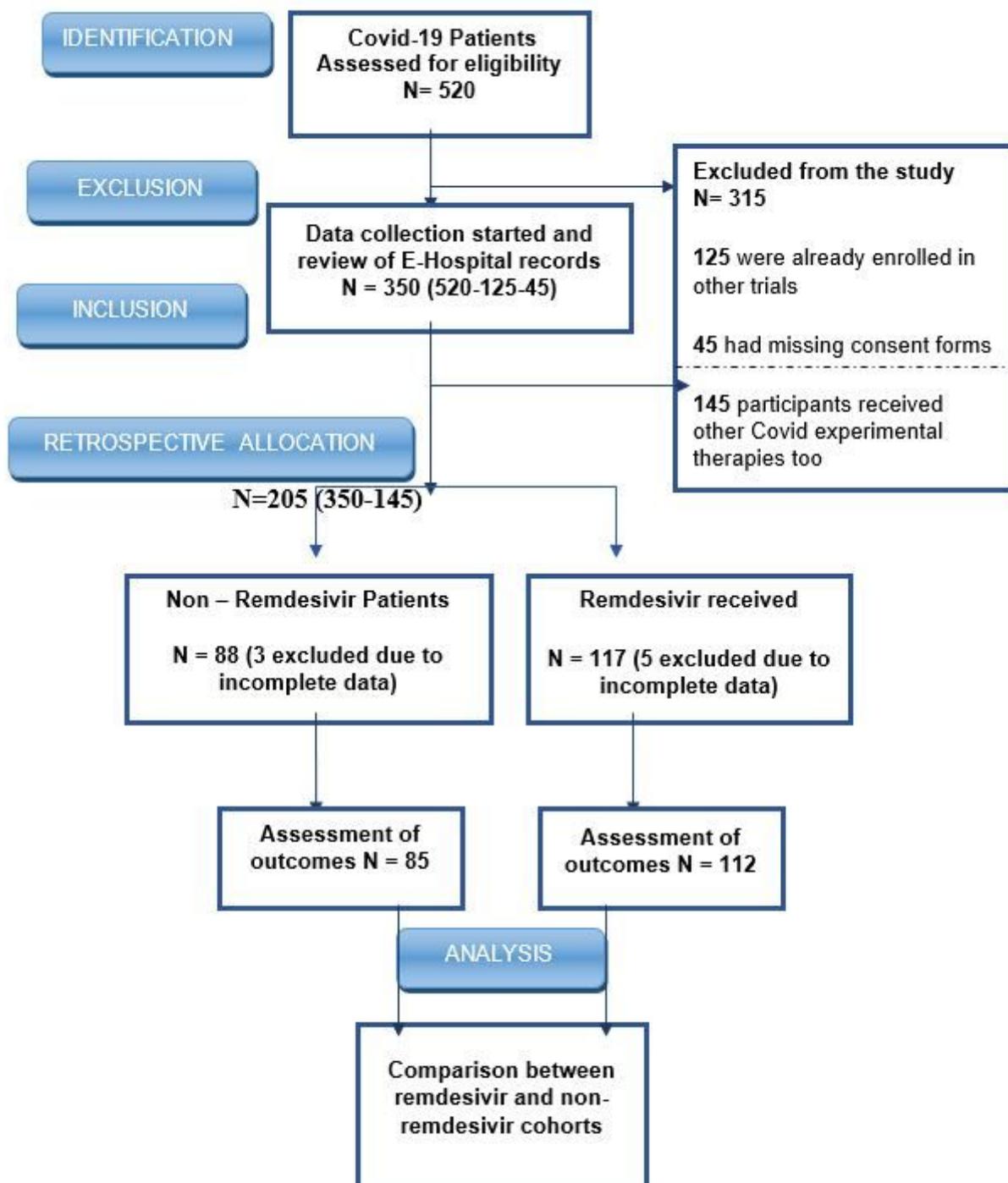


Figure 1

The study flow

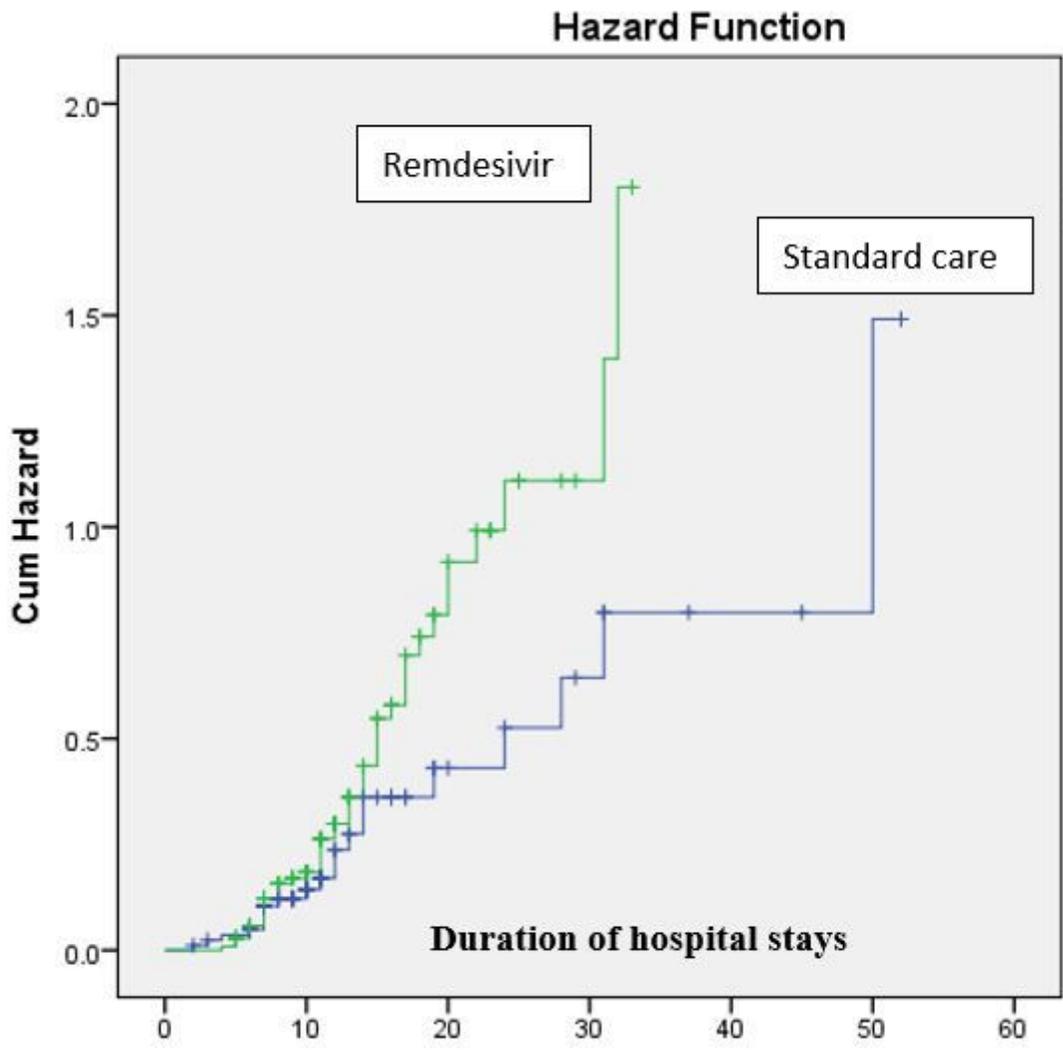


Figure 2

Kaplan Meier curves of remdesivir and standard care cohorts towards cumulative mortality