Assessing cardiac, hepatic, and renal safety of hospitalized Covid-19 patients treated with remdesivir: a retrospective cohort study

Author: Ajay Lakhisaran; **Daily supervisor:** Emiel Leegwater; **Referee:** Erik B. Wilms;
Examiner: Ewoudt M.W. van de Garde

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Abstract

Remdesivir played a major part as a treatment possibility of Covid-19 patients and still is part of treatment guidelines, however, there still are cardiac, hepatic, and renal safety concerns. The main aim of this research was to investigate cardiac-, hepatic and renal-related safety concerns in Covid-19 patients treated with remdesivir. To investigate these safety outcomes a retrospective cohort study was conducted. We included 2554 patients (male: 1449; female: 1105, remdesivir: 584; no-remdesivir: 1970) from the Haga Hospital, Leiden University Medical Center (LUMC), Alrijne Hospital and Haaglanden Medical Center (HMC) from the first of March 2020 until the first of March 2021. Bradycardia was seen in 8.3% of the remdesivir users compared to 6.1% in the no-remdesivir users (OR: 1.21; 95% CI: 0.80-1.83, p= 0.370). Acute kidney injury (AKI) was seen in 4.2% of the remdesivir users in comparison to 5.3% in no-remdesivir users (OR: 0.93; 95% CI: 0.54-1.59, p= 0.778). Acute liver injury was seen in 4.3% of the remdesivir users and in 1.1% of the no-remdesivir users (OR: 3.06; 95% CI: 1.62-5.76, p<0.001). Based on these findings there is no need to be concerned about the cardiac and renal outcomes of remdesivir. However, remdesivir still is associated with a higher likelihood on the occurrence of ALI.

Introduction

In December 2019, the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified [1]. The World Health Organization (WHO) declared the coronavirus disease 2019 (Covid-19) a global pandemic in March 2020 [2]. As of November 2022, more than six and a half million people have died due to Covid-19 [3]. During the Covid-19 pandemic remdesivir was the first direct antiviral treatment registered for hospitalized Covid-19 patients in the European Union. Because of the urgency of the Covid-19 pandemic remdesivir was introduced while limited data about effectiveness and safety in subgroups was available [4]. Based on findings of the Solidarity trial the World Health Organization (WHO) currently advises the use of remdesivir for patients with severe Covid-19 [5,6].

Remdesivir is an adenosine nucleotide prodrug which is intracellularly metabolized to the pharmacologically active remdesivir triphosphate. By acting as an analog of adenosine triphosphate (ATP) remdesivir triphosphate competes with the natural ATP substrate. This leads to the incorporation of remdesivir triphosphate into RNA by the SARS-CoV-2 RNA-dependent RNA polymerase, eventually resulting in a delayed chain termination of viral RNA during replication [7].

The Adaptive Covid-19 Treatment Trial (ACTT-1) showed that some of the patients treated with remdesivir recover faster leading to shorter hospitalization time. Taking the overall population into consideration patients treated with remdesivir recovered within approximately 11 days compared to the 15 days it took patients that received placebo to recover. Patients with a higher disease burden that needed supplemental oxygen also recovered faster (12 days) when treated with remdesivir compared to patients treated with placebo (18 days) [1].
A recent study by Gottlieb et al. (2022) showed that a 3-day remdesivir course decreases the risk of hospitalization or death related to Covid-19 by 87% in comparison to patients treated with placebo [8]. These trials have focused on the effectiveness of remdesivir as a treatment for Covid-19, which has resulted in safety outcomes remaining in the background. These trials also used selective patient groups leading to exclusion of certain patient groups and thus no real-world data was used.

A previous observational study suggested that reports of bradycardia were higher in Covid-19 patients treated with remdesivir compared to other drugs used for Covid-19 patients [9]. The remdesivir summary of product characteristics (SmPC) warns of an increase in transaminase levels caused by remdesivir [7]. Remdesivir safety studies also indicate an increase in transaminase levels caused by using remdesivir in Covid-19 patients [2,10]. A study done by Leiden University Medical Center (LUMC) concluded that there was a moderate increase of estimated glomerular filtration rate (eGFR), and no-severe elevations of alanine aminotransferase (ALT) were more prevalent than severe elevations in patients treated with remdesivir. This led to them recommending not taking renal and hepatic contraindications as absolute [10]. A more recent study found no significant association between remdesivir and acute kidney injury (AKI) or acute liver injury (ALI) [11]. Most of these earlier studies were conducted in small patient populations and there was no comparator group used.

Current research data about renal, hepatic, and cardiac safety of remdesivir use in Covid-19 patients is contradictory. Looking at these adverse events in a larger population would give extensive information about the incidence in the occurrence of these adverse events. This leads us to the main aim of this research which was to assess cardiac, hepatic, and renal safety of remdesivir used in the treatment of Covid-19 patients.

Methods

Study design, patient population and outcomes

This was a multi-center, retrospective cohort study. The population of this study consisted of hospitalized Covid-19 patients in the Haga Hospital, Leiden University Medical Center (LUMC), Alrijne Hospital and Haaglanden Medical Center (HMC) from the first of March 2020 until the first of March 2021. We received consent to use the data from the regional COVID committee of Leiden and The Hague including permission from the board of directors of the respective hospitals. Covid-19 was defined as patients having either a positive polymerase chain reaction (PCR) test, a covid diagnostic code or a COVID-19 Reporting and Data System (CO-RADS) score of 4 or higher. Patients that met at least one of the following criteria were excluded: (I) patients younger than 18 years; (II) patients that were admitted from another hospital; (III) patients without follow-up data; (IV) patients with missing baseline data for the respective outcome. Baseline for all patients was defined as laboratory values at t ≤ 0, time at 0 hours is the time the patient was admitted regarding Covid-19. (V) male patients with baseline ALT ≥225 U/l and female patients with baseline ALT ≥175 U/l; (VI) patients that were admitted to the ICU within 12 hours.

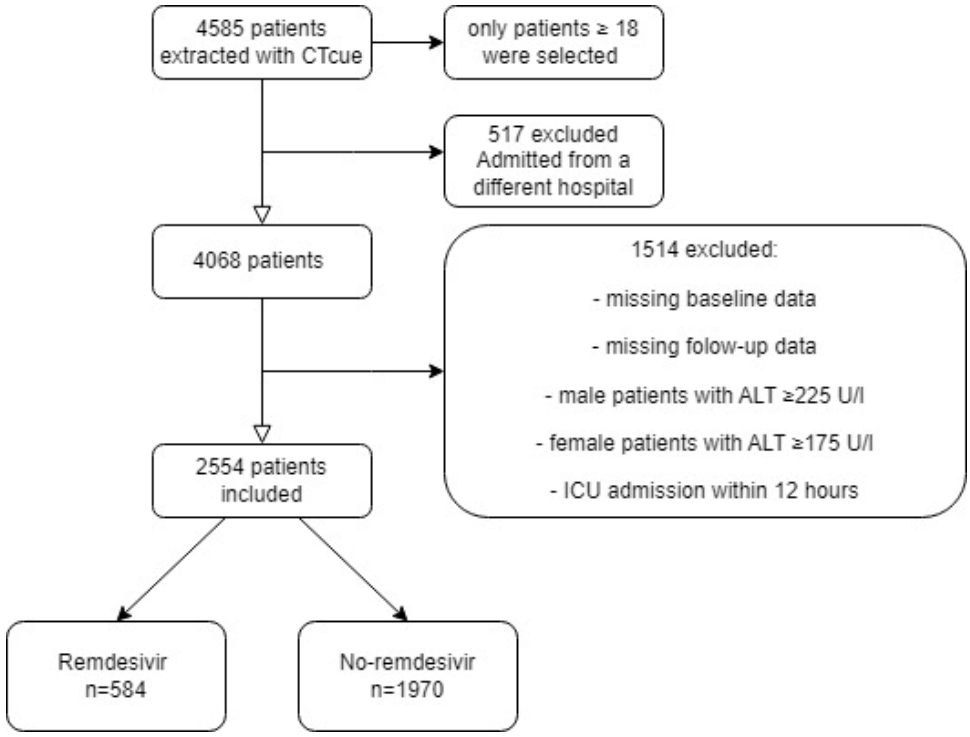

Figure 1. Flowchart: inclusion and exclusion.

To investigate the cardiac, renal, and hepatic safety of remdesivir we used the primary outcomes bradycardia, acute kidney injury (AKI) and acute liver injury (ALI). Bradycardia was defined as a heartrate ≤ 50bpm [12]. For the outcome bradycardia we excluded patients with a baseline heart rate ≤ 50 bpm. To determine which patients had AKI, the Kidney Disease: Improving Global Outcomes (KDIGO) classification was used. The KDIGO classification takes into consideration serum creatinine or estimated glomerular filtration rate (eGFR). According to KDIGO stage 1 AKI is defined as an increase in serum creatine of 1.5-1.9 times baseline value or an increase in serum creatinine of ≥ 26.5 mmol/l. Stage 2 AKI is defined as a 2-2.9-fold increase of serum creatinine from baseline. Stage 3 AKI is defined as an increase in serum

creatinine of 3 times or more or a serum creatinine ≥ 353.6 mmol/l or initiation of renal replacement therapy [13]. Data about urine output was not available therefore it was not taken into consideration. Patients with a delta ALT value of at least 2,5 times the upper limit of normal (ULN) were classified as patients with ALI. Delta ALT is the difference between follow-up ALT and baseline ALT. The ALT upper limit of normal is 45 U/l and 35 U/l respectively for male and female patients [14]. We also looked at four secondary outcomes namely ALT increase, aspartate aminotransferase (AST) increase, eGFR decrease and Urea increase. For these secondary outcomes we only looked at the fraction of the occurrence of these outcomes between remdesivir and no-remdesivir patients.

Data source and data selection

Patient data was extracted using CTcue. CTcue uses an Artificial Intelligence (AI) engine to extract and pseudonymize patient data from the Electronic Health Record (EHR) [15]. The data used in this research was extracted from EHR of Covid 19 patients admitted in the Haga Hospital, LUMC, Alrijne Hospital and HMC. The extracted data included admission and discharge data (such as admission origin, admission destination, discharge destination, admission and discharge date and time, etc.), sex, age, comorbidities, vitals (heart rate, body temperature, blood pressure, etc.), several laboratory data including baseline and follow-up (such as ALT, serum creatinine, AST, eGFR, etc.) and data regarding medication the patients received.

From the data extracted with CTcue relevant data regarding the outcomes was selected. In the data that was extracted laboratory values were taken at multiple time points. We therefore chose to take the lowest value of the heart rate and eGFR, the highest value of ALT, AST, serum creatinine and serum urea within the follow-up time of 15 days. We also did this for the baseline values. The 15-day follow-up time is based on a 5-to-10-day remdesivir cure including an additional 5 days to include late onset of adverse events. Baseline laboratory tests were taken while patients were in the emergency room. This happened mostly in the first 24 hours before 0 hours, which is the time the patients were in the emergency room or admitted for a different reason than Covid-19. The time at 0 hours is the time the patient was admitted regarding Covid-19. For the analysis of the outcomes only patients that had the respective baseline characteristics available were used. We used the relevant laboratory values regarding the outcome that was registered within the 15 days follow-up. We did not use laboratory values that were registered within the first 6 hours after administration of the first dose of remdesivir. Patients in the remdesivir group received at least one dose of remdesivir.

Analysis

To summarize patient characteristics and relevant laboratory values descriptive statistics were performed. While performing the descriptive statistics, a distinction was made between patients who received remdesivir and patients who did not receive remdesivir. Both continuous variables and dichotomous variables were used. For the comparison of continuous data, an independent-samples Mann-Whitney U test was performed and for the comparison of dichotomous data a chi-square test was performed. We presented continuous data as median and interquartile range (IQR), and dichotomous data was presented as absolute and relative frequencies.

Logistic regressions were performed to determine the influence of several independent factors on the outcome's bradycardia, ALI, and AKI. The results of these models were presented as odds ratio (OR) including a 95% confidence interval and the p-value. All the dependent variables that were analyzed are dichotomous therefore logistic regressions were performed. The logistic regressions were performed by looking at each independent variable in a

univariable model. This was done to see which variables have a significant association with the outcome. This was followed by forward inclusion in which we chose the independent variables from the univariable models that had a p-value < 0.05 and put them in a multivariable model. After this we performed backward deletion by removing the independent variables that did not come out as significant in the multivariable model and performed the multivariable analysis again. This was done for all the dependent variables. The independent variables used in the univariable, and multivariable analysis were either dichotomous or continuous. Continuous independent variables in the univariable and multivariable analysis show what the OR and 95% CI is for each increasing point of the respective variable.

For all the analyses a p-value <0.05 was considered statistically significant. SPSS statistics 28 was used to perform all statistical analyses during this research [16].

Sub analysis

A Logistic regression was performed to determine the influence of several independent factors on the outcome bradycardia after exclusion of patients admitted on the ICU. This sub analysis was also presented as the other logistic regressions.

Results

A total of 2554 patients were included, however not all these patients were used for every analysis of every outcome. These patients were used for at least one of the outcomes. For the analyses of the outcome bradycardia data of 2199 patients was used, for the outcomes ALI and ALT increase data of 2326 patients was used, for the outcomes AKI and eGFR data of 2222 patients was used and for the outcomes AST increase and Urea increase data of 2202 and 2400 patients was used, respectively. There was missing data regarding certain baseline patient characteristics. Results of the univariable analysis are presented in appendix 1(Table A1.).

Baseline patient characteristics and laboratory markers

Table 1 shows the patient characteristics at baseline and the most common medication the patients received and missing data. Of the 2554 patients that were included in this research 1449 were male and 1105 female. Of the 2554 patients 584 received remdesivir and the rest did not receive remdesivir during the entire follow up period. There was no significant difference between patients that received remdesivir and patients that did not regarding their age and sex. There was some missing data regarding baseline laboratory markers and regarding whether patients were smokers or not. A larger fraction of patients that received remdesivir (12.7%) were admitted to the ICU compared to patients that did not receive remdesivir (7.9%). The most frequent seen comorbidities were chronic heart disease, hypertension, and diabetes with a contribution of 312, 696 and 498 patients, respectively. Chronic kidney disease, kidney transplantation, diabetes and TB were the comorbidities with a statistically significant difference between patients that received remdesivir and patients that did not receive remdesivir. Baseline values of ALT, AST, heart rate, body temperature, oxygen saturation and CRP were statistically different between patients treated with remdesivir compared to patients that did not receive remdesivir. A higher fraction of patients treated with remdesivir also received dexamethasone (89.6%) and nadroparin (84.8%) compared to patients that did not receive remdesivir (43.5% and 73.8% respectively).

Table 1. Patient characteristics and laboratory markers at baseline

	Remdesivir			
	Yes	**No**	**p-value**	**Missing***
Age (years) — median (IQR)	67 (57-78)	69 (57-80)	0.064	
Male sex — n (%)	343 (58.7)	1106 (56.1)	0.267	
Smoker — n (%)	41 (9.0)	238 (14.5)	0.002	458
ICU admission — n (%)	74 (12.7)	156 (7.9)	<0.001	
Comorbidities — n (%)				
Chronic heart disease	65 (11.1)	247 (12.5)	0.362	
Hypertension	163 (27.9)	533 (27.1)	0.684	
Chronic lung disease	53 (9.1)	179 (9.1)	0.994	
Asthma	54 (9.2)	170 (8.6)	0.643	
Chronic kidney disease	21 (3.6)	113 (5.7)	0.042	
Kidney transplantation	7 (1.2)	9 (0.5)	0.046	
Chronic liver disease	1 (0.2)	10 (0.5)	0.276	
Diabetes	135 (23.1)	363 (18.4)	0.012	
HIV	0 (0.0)	7 (0.4)	0.149	
Tuberculosis	9 (1.5)	13 (0.7)	0.043	

Table 1. continuation				
	Remdesivir			
	Yes	No	p-value	Missing*
Baseline laboratory markers — median (IQR)				
ALT (U/L)	31 (21-47)	29 (21-45)	0.032	228
AST (U/L)	43 (31-60)	39 (29-57)	0.003	352
eGFR (ml/min/1,73 m^2)	72 (54-87)	72 (50-88)	0.991	332
Serum urea (mmol/L)	6.1 (4.6-8.9)	6 (4.4-9)	0.895	154
Heart rate (bpm)	92 (81-103)	90 (78-101)	0.048	355
Body temperature (°C)	38 (37.3-38.8)	37.7 (37-38.6)	<0.001	20
Oxygen saturation (%)	94 (90-96)	95 (92-97)	<0.001	42
Blood sodium (mmol/L)	136 (133-138)	136 (133-138)	0.964	76
Systolic BP (mmHg)	137 (122-154)	136 (121-152)	0.654	64
Diastolic BP (mmHg)	79 (70-88)	78 (68-88)	0.582	67
CRP (mg/L)	84.1 (46.7-136.3)	68 (29-125)	<0.001	104
Medication — n (%)				
Dexamethasone	523 (89.6)	857 (43.5)	0.000	
Hydroxychloroquine	2 (0.3)	93 (4.7)	<0.001	
Chloroquine	0 (0.0)	210 (10.7)	<0.001	
Nadroparin	495 (84.8)	1453 (73.8)	<0.001	
ACE inhibitor	82 (14.0)	225 (11.4)	0.087	
Angiotensin II receptor blocker	63 (10.8)	193 (9.8)	0.484	
Aminoglycosides	22 (3.8)	157 (8.0)	<0.001	
Beta-lactam antibiotics	191 (32.7)	1028 (52.2)	<0.001	
Macrolides	17 (2.9)	52 (2.6)	0.722	

* Total amount of patient data that was missing regarding the respective characteristic or laboratory marker. Abbreviations: IQR = Interquartile range; n = number; HIV= human immunodeficiency virus; ALT= alanine aminotransferase; AST= aspartate aminotransferase; U/L= Unit/liter; bpm= beats per minute; CRP= C-reactive protein; ACE= Angiotensin-converting enzyme.

Outcomes

Table 2 shows the total amount and fraction of patients that had the outcomes and what fraction of the patients had the outcome within the remdesivir and no-remdesivir groups. Of the 2199 patients used for the analysis of bradycardia 6.6% presented bradycardia (remdesivir 8.3%, no-remdesivir 6.1%, p=0.071). Patients treated with remdesivir showed a significant higher rate of ALI (remdesivir 4.3%, no-remdesivir 1.1%, p<0.001). An increase of ALT was seen more often in patients that received remdesivir (remdesivir 60%, no-remdesivir 15.9%, p<0.001). An increase of AST was seen in 39.3% of the patients that received remdesivir compared to 12.6% of the patients that did not receive remdesivir (p<0.001). There was no statistically significant higher occurrence of AKI between patients that received remdesivir versus patients that did not receive remdesivir (remdesivir 4.2%, no-remdesivir 5.3%, p<0.324). The rate of patients with a decrease of eGFR was significantly higher in patients that received remdesivir compared to patients that did not receive remdesivir (remdesivir 25.5%, no-remdesivir 20.2%, p=0.011). An increase of urea was seen in 78.3% of the patients that received remdesivir and 35% of the patients that did not receive remdesivir (p=0.011).

Table 2. Incidence of the outcomes				
Outcomes		**Remdesivir**		**p-value**
	Total	**Yes**	**No**	
Bradycardia* [2199]— n (%)				
Yes	146 (6.6)	44 (8.3)	102 (6.1)	0.071
ALI* [2326]— n (%)				
Yes	42 (1.8)	21 (4.3)	21 (1.1)	<0.001
ALT increase [2326]— n (%)				
Yes	584 (25,1)	291 (60.0)	293 (15.9)	<0.001
AST increase [2202]— n (%)				
Yes	397 (18)	176 (39.3)	221 (12.6)	<0.001
AKI* [2222] — n (%)				
Yes	112 (5.0)	21 (4.2)	91 (5.3)	0.324
eGFR decrease [2222] — n (%)				
Yes	476 (21.4)	128 (25.5)	348 (20.2)	0.011
Urea increase [2400] — n (%)				
Yes	1081 (45%)	437 (78.3)	644 (35.0)	<0.001

The number (n) and percentage (%) of patients with the outcome in the remdesivir and no-remdesivir groups. [] The total number of patients included in the analyses of the respective outcome. *Primary outcomes. Abbreviations: ALI= Acute Liver Injury; ALT= alanine aminotransferase; AST= aspartate aminotransferase; AKI= Acute Kidney Injury; eGFR= estimated glomerular filtration rate.

Bradycardia: logistic regression analysis

Table 3. Bradycardia: results of the logistic regression analysis.

Variables	**Multivariable analysis**	
	OR (95% CI)	**p-value**
Remdesivir	1.21 (0.80-1.83)	0.370
Age	1.02 (1.00-1.03)	0.026
Baseline heart rate	0.96 (0.95-0.97)	<0.001
Oxygen saturation	0.97 (0.95-0.996)	0.021
Systolic BP	0.99 (0.99-1.00)	0.068
Supplemental oxygen	1.02 (1.01-1.04)	0.014
Dexamethasone	2.06 (1.38-3.1)	<0.001
Beta lactam antibiotics	1.78 (1.15-2.61)	0.003
ICU admission	1.94 (1.15-3.26)	0.013

Results of the multivariable logistic regression analysis for the outcome bradycardia presented as OR (95%CI). Abbreviations: BP= blood pressure; OR= odds ratio; CI= confidence interval; ICU= intensive care unit.

The results of the multivariable logistic regression analysis regarding the outcome bradycardia are presented in table 3. The multivariable logistic regression analysis for the outcome bradycardia did not show significant association between the use of remdesivir and the occurrence of bradycardia (OR: 1.21; 95% CI: 0.80-1.83, p= 0.370). Increasing Age, increasing

amount of supplemental oxygen, dexamethasone, beta lactam antibiotics and ICU admission were the variables that showed to be associated with a higher chance on the occurrence of bradycardia. There was a lower likelihood of the occurrence of bradycardia while taking the variables increasing baseline heart rate and increasing oxygen saturation into consideration. The data also shows that increasing systolic BP was not significantly associated with lower likelihood of the occurrence of bradycardia.

Acute liver injury: logistic regression analysis

Table 4 shows the results of the multivariable logistic regression analysis regarding the outcome ALI. The multivariable analysis showed that there was a significantly higher association between the use of remdesivir and the occurrence of ALI (OR: 3.06; 95% CI: 1.62-5.76, p<0.001). The multivariable analysis also showed a significant higher chance of ALI while taking the variables increasing baseline ALT, increasing body temperature and ICU admission into consideration.

Table 4. Acute liver injury (ALI): results of the logistic regression analysis.

Variables	Multivariable analysis	
	OR (95% CI)	**p-value**
Remdesivir	3,06 (1,62-5,76)	<0.001
Baseline ALT	1.02 (1.01-1.02)	<0.001
Body temperature	1.45 (1.08-1.95)	0.013
ICU admission	5.37 (2.76-10.43)	<0.001

Results of the multivariable logistic regression analysis for the outcome ALI presented as OR (95%CI). Abbreviations: ALT= alanine aminotransferase; ICU= intensive care unit; OR= odds ratio; CI= confidence interval.

Acute kidney injury: logistic regression analysis

The results of the multivariable logistic regression analysis regarding the outcome AKI are presented in table 5. The multivariable logistic regression analysis regarding the outcome AKI did not show significant association between the use of remdesivir and the occurrence of AKI (OR: 0.93; 95% CI: 0.54-1.59, p= 0.778). Increasing baseline eGFR and increasing body temperature were the only two variables associated with a lower chance of AKI. The variables increasing systolic BP, kidney transplantation, aminoglycosides, beta lactam antibiotics and ICU admission showed to be associated with a higher chance of AKI.

Table 5. Acute kidney injury (AKI): results of the logistic regression analysis.

Variables	Multivariable analysis	
	OR (95% CI)	**p-value**
Remdesivir	0.93 (0.54-1.59)	0.778
Baseline eGFR	0.97 (0.96-0.98)	<0.001
Body temperature	0.79 (0.65-0.95)	0.012
Systolic BP	1.01 (1.01-1.02)	<0.001
Kidney transplantation	7.02 (2.26-21.83)	<0.001
Aminoglycosides	2.07 (1.18-3.63)	0.012
Beta lactam antibiotics	1.89 (1.18-3.04)	0.009
ICU admission	4.70 (2.84-7.78)	<0.001

Results of the multivariable logistic regression analysis for the outcome AKI presented as OR (95%CI). Abbreviations: eGFR= estimated glomerular filtration rate; BP= blood pressure; OR= odds ratio; CI= confidence interval; ICU= intensive care unit.

Bradycardia: sub analysis

The results of the multivariable logistic regression sub analysis regarding the outcome bradycardia are presented in appendix 2 (Table A2). The multivariable logistic regression sub analysis regarding the outcome bradycardia showed no significant association between the use of remdesivir and the occurrence of bradycardia (OR: 1.19; 95% CI: 0.77-1.85, p= 0.437). Increasing age, increasing amount of supplemental oxygen, dexamethasone, and beta lactam antibiotics were the variables that showed to be associated with a higher chance on the occurrence of bradycardia. An increase in baseline heart rate was associated with a lower chance of bradycardia.

Discussion

In this study we took a retrospective approach to investigate cardiac, hepatic, and renal safety outcomes in patients treated with remdesivir. We conducted this research in a cohort of 2554 Covid-19 patients hospitalized in Haga Hospital, Leiden University Medical Center (LUMC), Alrijne Hospital and Haaglanden Medical Center (HMC). This research showed no significant difference in the fraction of patients that developed bradycardia or AKI between the remdesivir group and no-remdesivir group. Remdesivir was not significantly associated with a difference in the likelihood on the occurrence of bradycardia or AKI.

We did find a significantly higher rate of ALI in the remdesivir group. The results also showed a higher likelihood on the occurrence of ALI in patients that received remdesivir in comparison to patients that did not receive remdesivir.

Increase of ALT, AST and urea were significantly more frequent in the remdesivir group compared to the group not receiving remdesivir. There also was a significant decrease of eGFR in the remdesivir group in comparison to the no-remdesivir group.

Intensive care patients are continuously monitored, especially their vitals. In case a patient on intensive care becomes bradycardic immediate intervention takes place to normalize their heart rate. This could lead to a distorted picture of the heart rate of patients admitted to the intensive care unit. Therefore, we performed a sub analysis regarding the outcome bradycardia while excluding patients admitted to the intensive care unit (Appendix 2.). The sub analysis showed no significant higher likelihood of bradycardia in patients treated with remdesivir (OR: 1.19; 95% CI: 0.77-1.85, p= 0.437). This supports our findings regarding the outcome bradycardia where patients admitted to the ICU were not excluded.

Findings put into perspective

There are differences in patient characteristics, baseline laboratory markers and the medications patients received between the remdesivir and no-remdesivir groups. The fraction of smokers was higher in the no-remdesivir group. This is possibly caused by the fact that there was missing data regarding smokers which is on its turn is caused by inadequate monitoring. The fraction of ICU admission was higher in the remdesivir group which could be an indication to patients who received remdesivir had a higher disease severity [17]. Baseline laboratory markers such as ALT, AST, heart rate, body temperature and oxygen saturation were significantly different between the remdesivir and no-remdesivir groups. However, these differences were so small when taking the median values in to regard that they most likely would not have resulted in a different clinical outcome.

Remdesivir was part of the treatment guidelines of Covid-19 patients from 12 years old with pneumonia requiring oxygen supplementation [4]. Dexamethasone was also a treatment possibility for patients Covid-19 patients requiring supplemental oxygen [18]. Therefore, it is likely that fraction of patients receiving dexamethasone is higher in the remdesivir group as seen in table 1, because these patients most likely had more severe Covid-19 and required supplemental oxygen.

The ACTT-1 trial showed that 1.3% of the remdesivir patients developed AKI in comparison to 2.3% of the patients receiving placebo [1]. This is also supported by the findings in our study. The ATCC-1 trial showed a higher fraction of patients had an increase of ALT and AST in the placebo group (ALT: 4.7%, AST: 6.4%) in comparison to the remdesivir group (ALT: 2.3%, AST: 3.4%) [1]. Our findings oppose these findings.

A more recent study by Lim et al., (2022) showed a significant association between remdesivir and a lower chance of AKI (OR: 0.40; 95% CI: 0.024 – 0.67, p<0.001). The study also found no significant association between treatment with remdesivir and the occurrence of ALI (OR: 0.68; 95% CI: 0.35 – 1.30, p= 0.241). For the outcome ALI the researchers of the study defined ALI as ALT 2.5 times ULN [11]. These findings are not in accordance with our findings. By defining ALI as 2.5 times ULN they did not take baseline values into consideration and thus making it unclear what the actual effect of remdesivir is on ALI.

Bradycardia has mostly been reported as separate cases. A previous pharmacovigilance study has shown that there is a significant association between remdesivir and the occurrence of bradycardia in Covid-19 patients compared to patients using tocilizumab, hydroxychloroquine, glucocorticoids, or lopinavir/ritonavir. This study used VigiBase® to get the data they analyzed. VigiBase® is a database that collects reports of suspected adverse drug reactions [9]. Among these suspected adverse drug reactions that are reported, some are reported by patients making the data used in this study sensitive for reporting bias. VigiBase® collects data from different countries and since it is not known which countries contributed to what amount of the data it is not possible to use this data to calculate the incidence of bradycardia being caused by remdesivir. As this research focused on reports on bradycardia not taking other variables into consideration it is still unclear whether bradycardia is caused by remdesivir use. Based on the findings of our research we can state that bradycardia is most likely not caused using remdesivir. This indicates towards another cause for the occurrence of bradycardia.

A previous study conducted by the Leiden University Medical Center (LUMC) showed a mild increase in transaminase levels in Covid-19 patients using remdesivir. An ALT elevation of ≥ 5 times ULN was seen in 2 of the 103 remdesivir users [10]. We found an ALT elevation from baseline of ≥ 2.5 times ULN in 21 of the 584 remdesivir users. Since Laar et al., (2021) did not use a comparator group it is unclear whether the increase in ALT is caused by remdesivir. Taking our findings in tot regard it is likely that the increase in ALT values as reported by Laar et al., (2021) are caused using remdesivir.

The study by Laar et al., (2021) also showed a decrease of eGFR in Covid-19 patients treated with remdesivir. However, this study included 103 patients without a comparator group and thus making it a small group of patients to base these findings on. Acute renal failure was also seen in patients using remdesivir as shown in a study by Gérard et al., (2021) conducted using data from VigiBase®. The study showed remdesivir to cause an increase in reporting of acute renal failure by approximately 20-fold compared to hydroxychloroquine, lopinavir/ritonavir, and tocilizumab [19]. The use of data from VigiBase® also makes the data of the study sensitive to selection bias. Our findings also show a significant difference in decrease of eGFR in the remdesivir group in comparison to the no-remdesivir group. However, when it comes to AKI there is no significant difference between the remdesivir and no-remdesivir group. This shows that remdesivir is associated with a decrease in kidney function but not enough to classify it as AKI.

SARS-CoV-2 expresses spike proteins which can eventually bind to Angiotensin converting enzyme 2 (ACE2) receptor. ACE2 is an enzyme that is expressed in several organs of humans such as the lungs, liver, kidney, and heart. By targeting ACE2 SARS-CoV-2 causes damage to these organs leading to multiple organ failure [20,21]. Taking this and the findings of our study and previous research into consideration it is more likely that bradycardia and AKI are a result of multiple organ failure caused by SARS-CoV-2. Therefore, resulting in no significant difference of the occurrence of AKI and bradycardia between patients that received remdesivir and patients that did not.

The strength of this research lies in the fact that we included 2544 patients, making this a relatively large population compared to previous studies. Another strength of our research is the use of real-world data. We also based our outcomes in a way taking baseline parameters in regard, leading to a more accurate estimation of the actual safety outcomes. Since we have chosen a retrospective approach, there are limitations that come with this approach such as possible confounders and absence of data. A main limitation of this study is that data regarding cardiac medication was not fully available. Therefore, we were not able to assess whether cardiac medication could influence the outcome bradycardia. Taking into regard that there were significant differences in the remdesivir and no-remdesivir groups we performed univariable logistic regression analysis to see whether the variables are associated with the outcome. Hereafter we performed multivariable logistic regression using a forward inclusion and backward deletion method correcting for possible confounders. The data that was collected was done while remdesivir was new for the indication Covid-19. Therefore, it is possible that patients that received remdesivir were monitored more frequent. However, Covid-19 itself was very new disease at that time with lots of uncertainties. Patients with Covid-19 were very well monitored making it less likely that monitoring was different in remdesivir and no-remdesivir users.

As we found no significant increase in the occurrence of bradycardia and AKI additional monitoring of cardiac and kidney function is not necessary in patients that are treated with remdesivir. With monitoring of kidney function remdesivir could be used. Monitoring of cardiac and kidney function already happens due to a possible decline caused by Covid-19 itself. Based on our findings patients that receive remdesivir are more likely to have an increase of ALT of ≥ 2.5 times ULN from baseline. Based on this we advise monitoring of transaminase levels in Covid-19 patients that receive remdesivir.

Conclusion

When it comes to bradycardia or acute kidney injury the use of remdesivir does not seem to be a concern based on the findings of this study. The data did not show remdesivir to be associated with a higher likelihood on the occurrence of bradycardia or acute kidney injury. However, based on the findings in this study we still see hepatic safety concerns regarding remdesivir. The use of remdesivir is associated with a higher likelihood of the occurrence of acute liver injury.

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References

1. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. New England Journal of Medicine. 2020 Nov 5;383(19):1813–26.
2. Gupte V, Hegde R, Sawant S, Kalathingal K, Jadhav S, Malabade R, et al. Safety and clinical outcomes of remdesivir in hospitalised COVID-19 patients: a retrospective analysis of active surveillance database. BMC Infectious Diseases. 2022 Jan 4;22(1).
3. World Health Organization. WHO COVID-19 dashboard [Internet]. World Health Organization. 2022. Available from: https://covid19.who.int/
4. CZARSKA-THORLEY D. First COVID-19 treatment recommended for EU authorisation [Internet]. European Medicines Agency. 2020. Available from: https://www.ema.europa.eu/en/news/first-covid-19-treatment-recommended-eu-authorisation
5. WHO Solidarity Trial Consortium. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. The Lancet [Internet]. 2022 May 2;0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00519-0/fulltext
6. Therapeutics and COVID-19: Living guideline, 16 September 2022 [Internet]. www.who.int. 2022. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.5
7. ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS [Internet]. [cited 2022 Oct 24]. Available from: https://www.ema.europa.eu/en/documents/product-information/veklury-epar-product-information_en.pdf
8. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. New England Journal of Medicine. 2021 Dec 22;386(4).
9. Touafchia A, Bagheri H, Carrié D, Durrieu G, Sommet A, Chouchana L, et al. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns. Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases [Internet]. 2021 Feb 27;27(5): S1198-743X (21)00094X. Available from: https://pubmed.ncbi.nlm.nih.gov/33647441/
10. Laar SA, Boer MGJ, Gombert-Handoko KB, Guchelaar H, Zwaveling J. Liver and kidney function in patients with Covid-19 treated with remdesivir. British Journal of Clinical Pharmacology. 2021 Mar 25;87(11).
11. Lim H, Palaiodimos L, Berto CG, Tedunjaiye O, Malik P, Nagraj S, et al. Remdesivir in the Treatment of COVID-19: A Propensity Score-Matched Analysis from a Public Hospital in New York City Assessing Renal and Hepatic Safety. Journal of Clinical Medicine. 2022 May 31;11(11):3132.
12. Bradycardie | Hart+Vaat Centrum [Internet]. hartenvaatcentrum.mumc.nl. [cited 2022 May 3]. Available from: https://hartenvaatcentrum.mumc.nl/aandoeningen/bradycardie

13. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements. 2012 Mar;2(1):1.
14. Zoek een test | NVKC [Internet]. www.nvkc.nl. [cited 2022 May 3]. Available from: https://www.nvkc.nl/zoek-een-test/?id=132
15. CTcue - Empowering healthcare with real-world evidence [Internet]. ctcue.com. 2020 [cited 2022 Nov 4]. Available from: https://ctcue.com/
16. SPSS Statistics - Overview [Internet]. www.ibm.com. [cited 2022 Nov 4]. Available from: https://www.ibm.com/nl-en/products/spss-statistics?mhsrc=ibmsearch_a&mhq=spss
17. Sadeghi A, Eslami P, Dooghaie Moghadam A, Pirsalehi A, Shojaee S, Vahidi M, et al. COVID-19 and ICU admission associated predictive factors in Iranian patients. Caspian Journal of Internal Medicine [Internet]. 2020 [cited 2022 Oct 8];11(Suppl 1):512–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7780877
18. EMA. EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation - European Medicines Agency [Internet]. European Medicines Agency. 2020. Available from: https://www.ema.europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation#:~:text=More%20about%20the%20medicine&text=Dexamethasone%20was%20first%20considered%20a
19. Gérard AO, Laurain A, Fresse A, Parassol N, Muzzone M, Rocher F, et al. Remdesivir and Acute Renal Failure: A Potential Safety Signal From Disproportionality Analysis of the WHO Safety Database. Clinical Pharmacology and Therapeutics [Internet]. 2021 Apr 1 [cited 2021 Nov 11];109(4):1021–4. Available from: https://pubmed.ncbi.nlm.nih.gov/33340409/
20. Zhao W, Li H, Li J, Xu B, Xu J. The mechanism of multiple organ dysfunction syndrome in patients with COVID-19. Journal of Medical Virology. 2022 Feb 8;94(5):1886–92.
21. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Critical Care [Internet]. 2020 Jul 13;24(1). Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03120-0

Appendices

Appendix 1: Results of the univariate analyses

Table A1. Results of the univariable logistic regression analysis.

Variables	Bradycardia		Acute liver injury (ALI)		Acute kidney injury (AKI)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Remdesivir	1.402 (0.971-2.026)	0.072	3.922 (2.124-7.243)	<0.001	0.784 (0.482-1.273)	0.325
Female	0.759 (0.537-1.073)	0.118	0.411 (0.201-0.839)	0.015	1.179 (0.805-1.726)	0.398
Age	1,026 (1,013-1,038)	<0.001	0.982 (0.963-1.000)	0.053	1.031 (1.017-1.046)	<0.001
Baseline heart rate	0.963 (0.952-0.974)	<0.001	n/a	n/a	n/a	n/a
Baseline ALT	n/a	n/a	1.016 (1.009-1.023)	<0.001	n/a	n/a
Baseline eGFR	n/a	n/a	n/a	n/a	0.969 (0.961-0.976)	<0.001
Temperature	1.031 (0.885-1.202)	0.692	1.567 (1.180-2.081)	0.002	0.796 (0.667-0.951)	0.012
Oxygen saturation	0.970 (0.949-0.991)	0.006	1.032 (0.964-1.105)	0.358	0.984 (0.957-1.013)	0.280
Blood sodium	1.039 (0.997-1.082)	0.067	0.969 (0.900-1.042)	0.395	0.784 (0.482-1.273)	0.325
Systolic BP	0.991 (0.984-0.998)	0.013	0.993 (0.980-1.006)	0.261	1.009 (1.002-1.017)	0.016
Diastolic BP	0.987 (0.976-0.998)	0.025	0.998 (0.978-1.017)	0.810	1.008 (0.997-1.020)	0.158
Chronic heart disease	1.832 (1.201-2.795)	0.005	0.724 (0.256-2.043)	0.541	2.043 (1.294-3.226)	0.002
Hypertension	1.159 (0.805-1.669)	0.427	0.602 (0.277-1.307)	0.199	1.048 (0.693-1.584)	0.826
Chronic kidney disease	2.029 (1.129-3.644)	0.018	0.432 (0.059-3.169)	0.409	4.790 (2.912-7.880)	<0.001
Diabetes	1.369 (0.925-2.027)	0.116	0.422 (0.150-1.188)	0.102	1.728 (1.139-2.621)	0.010

Table A1. Continuation

Variables	Bradycardia		Acute liver injury (ALI)		Acute kidney injury (AKI)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Smoking	0.946 (0.557-1.606)	0.838	0.466 (0.111-1.963)	0.298	1.585 (0.944-2.660)	0.081
Tuberculosis	1.487 (0.343-6.446)	0.596	2.761 (0.362-21.064)	0.327	0.991 (0.132-7.473)	0.993
Kidney transplantation	1.409 (0.179-11.083)	0.745	n/a	n/a	13.214 (4.618-37.808)	<0.001
Supplemental oxygen	1.030 (1.012-1.048)	0.001	1.030 (1.007-1.054)	0,011	1.023 (1.006-1.040)	0.009
Dexamethasone	2.347 (1.627-3.385)	<0.001	1.321 (0.705-2.475)	0.386	0.635 (0.433-0.931)	0.020
Hydroxychloroquine	0.474 (0.148-1.517)	0.209	0.595 (0.081-4.371)	0.609	1.156 (0.459-2.910)	0.759
Chloroquine	0.425 (0.185-0.976)	0.044	1.826 (0.760-4.389)	0.178	1.930 (1.127-3.307)	0.017
Nadroparin	1.37 (0.900-2.101)	0.141	4.084 (1.257-13.267)	0.019	0.676 (0.448-1.021)	0.063
ACE-inhibitors	0.957 (0.559-1.637)	0.872	2.009 (0.951-4.244)	0.067	1.588 (0.962-2.622)	0.07
ARB	0.937 (0.520-1.687)	0.827	0.918 (0.325-2.594)	0.871	2.088 (1.272-3.427)	0.004
Aminoglycosides	1.205 (0.652-2.228)	0.552	3.188 (1.451-7.003)	0.004	3.781 (2.315-6.174)	<0.001
Beta lactam antibiotics	1.859 (1.311-2.638)	<0.001	2.007 (1.062-3.792)	0.032	2.738 (1.814-4.133)	<0.001
Macrolides	1.392 (0.547-3.543)	0.488	5.477 (2.073-14.468)	<0.001	2.747 (1.216-6.205)	0.015
ICU admission	2.322 (1.444-3.733)	<0.001	7.281 (3.834-13.826)	<0.001	4.761 (3.052-7.427)	<0.001
CRP	1.002 (1.000-1.004)	0.069	1.003 (1.000-1.007)	0.034	1.000 (0.998-1.003)	0.971

Abbreviations: IQR = Interquartile range; n = number; OR= odds ratio; CI= confidence interval; HIV= human immunodeficiency virus; ALT= alanine aminotransferase; AST= aspartate aminotransferase; U/L= Unit/liter; bpm= beats per minute; ACE= Angiotensin-converting enzyme; ARB= angiotensin ll receptor blocker; CRP= C-reactive protein, ICU= intensive care unit.

Appendix 2. Bradycardia: sub analysis

Table A2. Bradycardia sub analysis: results of the logistic regression analysis.

Variables	Multivariable analysis	
	OR (95% CI)	**p-value**
Remdesivir	1.19 (0.77-1.85)	0.437
Age	1.01 (1.00-1.03)	0.042
Baseline heart rate	0.96 (0.95-0.98)	<0.001
Supplemental oxygen	1.03 (1.01-1.05)	0.004
Dexamethasone	2.00 (1.32-3.02)	0.001
Beta lactam antibiotics	1.67 (1.14-2.47)	0.009

Results of the multivariable logistic regression sub analysis for the outcome bradycardia presented as OR (95%CI). Abbreviations: OR= odds ratio; CI= confidence interval.