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Safety of remdesivir in the treatment of acute SARS-CoV-2 infection in pediatric patients

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Abstract

Background Transaminase and creatinine elevations have been well described in adults treated with remdesivir for COVID-19. It is hypothesized that a similar safety profile exists in children with COVID-19 treated with remdesivir, but available data are limited, especially in children < 12 months. The primary aim of this study was to determine the prevalence and timing of elevations in transaminases and creatinine in children with COVID-19 who were treated with remdesivir.

Methods This was a retrospective, observational cohort study including all pediatric patients admitted to a single, freestanding children's hospital who were positive for COVID-19 and received at least 1 dose of remdesivir between 1/1/2020 and 5/31/2022. Available baseline and peak transaminase and creatinine concentrations were evaluated. Multivariable logistic regression analysis was performed to identify risk factors for transaminase elevation.

Results A total of 180 patients met inclusion criteria. Creatinine elevation of any grade was noted in 16% and remained elevated only in those with underlying chronic kidney disease. Transaminase elevation of any grade was noted in 58% of patients and remained elevated in only 1%. Older age and critical respiratory disease were associated with higher risk of significant transaminase elevation, whereas non-Hispanic ethnicity was strongly associated with protection against significant transaminase elevation.

Conclusions In our cohort of hospitalized children with COVID-19 who were treated with remdesivir, most patients experienced only mild transaminitis and normal creatinine concentrations. A limited number of patients experienced laboratory abnormalities which were transient, suggesting a favorable safety profile for remdesivir use in pediatrics.

Keywords Children, COVID-19, Anti-viral, Side effects, Remdesivir

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Background

Coronavirus Disease 2019 (COVID-19), the illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019, swiftly progressing to a global pandemic. Since the onset of the pandemic, over 15 million children have tested positive for COVID-19 in the United States [1]. While most children are asymptomatic or experience only mild symptoms, more severe disease and hospitalization can occur, especially in children with comorbidities [2, 3]. The anti-viral, remdesivir, acts by inhibiting the SARS-CoV-2 viral RNA polymerase and remains the primary therapeutic option for COVID-19 in children. In May 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the use of remdesivir in adult and pediatric patients ≥ 12-years-old and ≥ 40-kilograms (kg), which was later expanded to young children; its use was formally approved in October 2020. It was not until April 2022 that the FDA approved use of the anti-viral in pediatric patients ≥ 28-days-old and weighing at least 3-kg. Studies demonstrated that remdesivir use decreased time to recovery in hospitalized adults [4] and decreased risk of hospitalization and death in adults with COVID-19 treated as outpatients [5]. The most common side effects reported in adults were elevations in aspartate transaminase (AST) and alanine transaminase (ALT) [6, 7]. However, there remains limited safety data for remdesivir in pediatric patients. One multicenter study of 77 pediatric patients with severe COVID-19 and treated with remdesivir demonstrated increased transaminases as a common side effect with AST elevated in 55% and ALT elevated in 48% of the study population [8]. In contrast, another single center study of 48 pediatric patients demonstrated no hepatic or renal toxicity [9]. Preliminary data from the phase 2/3 multicenter trial of remdesivir use in pediatric patients 28-days to 18-years-old demonstrated elevated ALT in only 4 of the 53 patients enrolled [10, 11]. As remdesivir moved from EUA to FDA-approved, and with increased use since the start of the pandemic [12], understanding its side effects is imperative. This study aimed to determine the prevalence and timing of elevations in transaminases and creatinine in pediatric patients with COVID-19 who were treated with remdesivir, including patients aged < 12 months, to improve treatment and monitoring recommendations.

Methods

This retrospective observational cohort study was conducted at a large, 298-bed, freestanding children's hospital in the upper Midwest. The electronic health record (EHR; Epic systems, Verona, WI, USA) was queried for pediatric patients hospitalized between January 1, 2020, and May 31, 2022, with diagnosis codes consistent with SARS-CoV-2 infection. All patients who received at least one dose of remdesivir during their hospital stay were included. Data was collected by retrospective chart review and stored using Research Electronic Data Capture (REDCap), a secure, web-based software platform for data capture [13]. The dataset generated and analyzed during the current study is not publicly available as it contains protected health information, but the de-identified dataset is available from the corresponding author on reasonable request. The study was reviewed by the Children's Wisconsin Human Research Protection Program Institutional Review Board. As it is a retrospective observational cohort study, it was determined to not be human subject's research and the review board waived the need for consent. Clinical trial number: not applicable.

Data collected and definitions

Variables collected through chart review included sex, race, ethnicity, age at time of admission, duration of remdesivir therapy, respiratory disease severity at remdesivir initiation, presence of underlying high risk medical conditions, and baseline and peak AST, ALT, and creatinine concentrations. Disease severity was based on the National Institute of Health COVID-19 treatment guidelines [14] and defined by the level of respiratory support above baseline required by each patient at the time of remdesivir initiation. Moderate respiratory disease was defined as hospitalization without requiring respiratory support. Severe respiratory disease was defined as requiring either low or high flow oxygen support. Critical respiratory disease was defined as requiring non-invasive (CPAP / BiPAP), invasive (ventilatory), or extracorporeal membrane oxygenation support. Patients that required inotropic support were included in the study and were placed in the disease severity category based on their respiratory support requirements.

Obesity or overweight was defined as weight in kilograms ≥ 95th percentile for age at the time of admission or a documented history of obesity as a pre-existing medical problem. All other underlying high-risk medical conditions were defined in accordance with the Centers for Disease Control and Prevention [15].

Baseline AST, ALT, and creatinine were defined as the concentration measured temporally closest to remdesivir initiation between 7 days prior to and 4 h after the first dose of remdesivir. Normal concentrations of AST, ALT, and creatinine were based on age (Supplemental Table). Peak concentration was defined as the highest value for AST, ALT, and creatinine documented, from baseline value through 30 days after remdesivir initiation. We categorized AST, ALT, and creatinine elevations based on the Division of AIDS categories for grading the severity of adverse events [16]. For AST and ALT, values were categorized as grade 1–2 (mild-moderate) if

the peak concentration of either enzyme was between the upper limit of normal (ULN) for age to <5 times the ULN, grade 3 (severe) if the peak concentration was ≥5 times but <10 times the ULN for age, and grade 4 (potentially life threatening) if the peak concentration was ≥10 times the ULN. For creatinine, grade 1 (mild) elevation was any elevation of creatinine to 1.3 times the ULN, grade 2 (moderate) was >1.3 to 1.8 times the ULN, grade 3 (severe) was >1.8 to <3.5 times the ULN, and grade 4 (potentially life threatening) was ≥3.5 times the ULN.

Statistical analysis

Categorical variables are reported as the number (N) and continuous variables are reported as median (interquartile range (IQR)). Statistical significance between variables was measured by Fisher's Exact Test for categorical variables and Mann-Whitney test for continuous variables. Logistic regression analysis was performed to examine the association between each potential risk factor (age, sex, race, ethnicity, respiratory disease severity, high-risk underlying condition(s), and duration of remdesivir) and any elevation of AST, ALT, or creatinine. Multivariable logistic regression analysis was performed including all potential risk factors in the model. In cases of separability, Firth's penalized maximum likelihood estimation was performed to reduce bias in parameter estimation [17]. Odds ratio (OR) or adjusted OR (aOR) and 95% confidence interval (CI) were generated. The association between each potential risk factor and grade 3–4 elevation of AST, ALT, or creatinine was assessed in a similar manner. A p-value<0.05 was considered significant. Data were analyzed using SPSS version 28 (Chicago, IL, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Demographics

In total, 180 patients met study inclusion criteria (Table 1). Median age was 10.5 years (IQR 2.8, 15.3; range 0 days to 22 years) at the time of hospital admission; 29 patients (16%) were aged≤12 months. Eighty-one patients (45%) were female, 110 (61%) were White/Caucasian, and 52 (29%) were Black/African American. Thirty-nine (22%) patients identified as Hispanic. One-hundred forty-three (79%) patients had at least 1 high-risk condition: most common were chronic lung disease (43%), neurodevelopmental or genetic conditions (37%), technology dependence (29%), and overweight/obesity (26%). Of the 180 patients, 47 (26%) had moderate respiratory disease, 110 (61%) had severe respiratory disease, and 23 (13%) had critical respiratory disease at the time of remdesivir initiation. Of the 180 patients, 3 patients died during the admission in which they received remdesivir: 1 from bacterial sepsis, 1 from respiratory failure, and 1 from multisystem inflammatory syndrome in children (MIS-C) secondary to COVID-19.

Remdesivir course

Median duration of remdesivir therapy was 1-day (IQR 1, 5; range 1–10 days); 93 (52%) patients received 1–3 days, 23 (13%) received 4 days, and 64 (36%) received≥5 days of remdesivir. The reasons for discontinuing remdesivir were completion of the intended course for 78 patients (43%), discharge from the hospital for 60 patients (33%), no longer hypoxic for 20 patients (11%), and death for 2 patients (1%). For the remaining 13 patients, the reasons for discontinuing remdesivir included parent preference, clinical improvement, repeat negative COVID testing, lost intravenous access, or were unknown. Clinician documentation of elevated transaminases as the reason for discontinuing remdesivir occurred for 6 patients. Only one patient had an adverse reaction which manifested as urticaria concerning for allergic reaction shortly after remdesivir was administered. Vitals remained stable and rash spontaneously resolved prior to intervention and the patient did not receive additional doses of remdesivir.

Prevalence and timing of creatinine elevations

Of the 180 patients, 176 had creatinine measured. Twenty-four had only baseline creatinine checked (2 with grade 1 elevation, 22 normal) and 152 had creatinine measured both at baseline and after remdesivir initiation. Of the 176 patients with creatinine measured, 148 (84%) had peak creatinine that was normal. Twenty-eight (16%) had any elevation in creatinine; 15 (9%) grade 1, 5 (3%) grade 2, 5 (3%) grade 3, and 3 (2%) grade 4. All patients with grade 1 creatinine elevation returned to normal. Of the 13 patients with ≥grade 2 elevation, creatinine returned to normal in 9 and remained elevated in 4 patients, all of whom had a previous history of kidney disease. Of all patients with creatinine measured, creatinine elevation occurred prior to or on the day of remdesivir initiation in 10% and after remdesivir in 7%. The timing of post-remdesivir creatinine elevation was the day after remdesivir was started for 3, two days after initiation for 3, three days after initiation for 1, four days after initiation for 1, and >1 week after initiation for 2 patients. Median age of patients with elevated baseline creatinine was 13.6 years (8.9, 15.8).

Prevalence and timing of transaminase elevations

Of the 180 patients, 177 had transaminases measured with 151 checked both at baseline and after remdesivir initiation. Of the 177 patients with transaminases measured, 75 (42%) had normal transaminases with every measurement, 42 (24%) had peak transaminase elevation at baseline, and 60 (34%) had peak transaminase elevation after remdesivir was started. Of the 102 patients

Table 1 Cohort demographics and clinical characteristics*

	Study Population[a]	Creatinine					AST / ALT				
		Normal creatinine	Any elevated creatinine (> ULN)	p-value	Grade 3–4 elevation creatinine (> 1.8 x ULN)	p-value	Normal AST and ALT	Any elevated AST or ALT at peak (> ULN)	p-value	Grade 3–4 elevation AST or ALT at peak (≥ 5x ULN)	p-value
Total number of patients	180	148	28		8[b]		75	102		14[c]	
Sex				0.84		0.99			0.76		0.99
Male	99 (55)	79 (53)	16 (57)		4 (50)		40 (53)	57 (56)		7 (50)	
Female	81 (45)	69 (47)	12 (43)		4(50)		35 (47)	45 (44)		7 (50)	
Race				0.91		0.44			0.52		0.60
African American	52 (29)	41 (30)	8 (35)		4 (50)		26 (35)	25 (25)		3 (21)	
Caucasian	110 (61)	94 (67)	15 (65)		4 (50)		46 (61)	63 (62)		9 (64)	
Asian	3 (2)	3 (2)	0 (0)		0		1 (1)	1 (1)		0	
Multiracial	2 (1)	2 (1)	0 (0)		0		0	2 (2)		0	
Unknown/Missing	13 (7)						2 (3)	11 (11)		2 (14)	
Ethnicity				0.99		0.68			0.04		0.005
Hispanic	39 (22)	33 (23)	6 (23)		1 (13)		11 (15)	28 (27)		7 (50)	
Non-Hispanic	132 (73)	108 (77)	20 (77)		7 (87)		62 (83)	**67 (66)[d]**		**6 (43)[d]**	
Unknown/Missing	9 (5)						2 (3)	7 (7)		1 (7)	
Age at admission (years)	10.5 (2.8, 15.3)	10.1 (2.6, 15.2)	13.0 (7.3, 15.5)	0.31	11.2 (0.6, 15.8)	0.85	5.0 (1.2, 12.1)	**13.3 (8.3, 16.3)[e]**	< 0.001	13.8 (11.0, 17.2)	0.003
Age at admission				0.58		0.63			0.021		0.28
<12 months	29 (16)	25 (17)	3 (11)		2 (25)		17 (23)	10 (10)		1 (7)	
≥12 months	151 (84)	123 (83)	25 (89)		6 (75)		58 (77)	92 (90)		13 (93)	
Presence of high-risk underlying condition[f]	143 (79)	117 (79)	23 (82)	0.80	6 (75)	0.68	56 (75)	86 (84)	0.19	10 (71)	0.75
Respiratory disease severity at remdesivir initiation[g]				< 0.001		0.008			0.09		0.07
Moderate respiratory disease	47 (26)	40 (27)	6 (22)		1 (13)		20 (27)	27 (26)		3 (21)	
Severe respiratory disease	110 (61)	96 (65)	11 (39)		3 (37)		50 (67)	57 (56)		7 (50)	

Table 1 (continued)

	Study Population[a]	Creatinine					AST / ALT					
		Normal creatinine	Any elevated creatinine (> ULN)	p-value	Grade 3–4 elevation creatinine (> 1.8 x ULN)	p-value	Normal AST and ALT	Any elevated AST or ALT at peak (> ULN)	p-value	Grade 3–4 elevation AST or ALT at peak (≥ 5x ULN)	p-value
Critical respiratory disease	23 (13)	12 (8)	11 (39)		4 (50)		5 (6)	18 (18)		4 (29)	
Duration of remdesivir therapy, days	1 (1, 5)	1 (1,5)	2.5 (1.0, 5.0)	0.64	4.5 (1.0, 5.0)	0.43	1 (1, 5)	4 (1, 5)	0.41	1 (1, 5)	0.67

*n (%) or median (IQR) were presented

[a] Three of the 180 patients had no documented AST or ALT. Baseline AST was also the peak for 95 patients, 25 of whom had no repeat AST checked (7 grade 1–2 elevation and 18 normal). Baseline ALT was also the peak for 99 patients, 26 of whom had no repeat ALT checked (6 grade 1–2 elevation, 20 normal). Transaminases were followed after remdesivir in 151 patients with peak AST occurring at baseline in 69 (46%) and peak ALT occurring at baseline in 73 (48%)

[b] These patients represent a subset of the "Any elevated creatinine at peak (> ULN)" group

[c] These patients represent a subset of the "Any elevated AST or ALT at peak (> ULN)" group

[d] Compared to normal AST and ALT by Fisher's exact test

[e] Compared to normal AST and ALT by Mann-Whitney test

[f] Patients could have ≥ 1 high-risk condition which included: chronic lung disease 62 (43%), neurodevelopmental or genetic 53 (37%), technology dependence 42 (29%), obesity / overweight 37 (26%), immunocompromised host 21 (15%), cardiovascular disease 22 (15%), chronic kidney disease 8 (6%), sickle cell disease or thalassemia 7 (5%), diabetes 6 (4%), chronic liver disease 2 (1%), stroke or cerebrovascular disease 1 (1%), other 2 (1%)

[g] One patient with moderate respiratory disease and 8 patients with severe respiratory disease required pressor support

with transaminase elevation, 88 (86%) had mild-moderate, grade 1–2 elevation and 14 (14%) had grade 3–4 peak transaminase elevation. Of the 14 patients with grade 3–4 peak transaminase elevation, 12 had elevation at baseline. Twelve (86%) were aged ≥ 9 years. Two patients were aged < 2 years; 1 was < 12-months and positive for three respiratory viruses at admission and the other was diagnosed with MIS-C secondary to COVID-19 which was identified as the cause of death. Transaminases down trended to grade 1–2 or returned to normal in 12 of the 14 patients and remained elevated in 2 patients. One patient was diagnosed with viral myocarditis and continued to demonstrate elevation of ALT at discharge. The other patient's transaminases remained elevated at discharge, and it is not known if transaminitis resolved after discharge.

Associations of elevations of creatinine and transaminases

Comparison of demographic and clinical variables showed that the only association with elevated creatinine was illness severity at the time of remdesivir initiation, with more severe respiratory disease associated with higher grade creatinine elevation (Table 1). Patients with any elevation in transaminases were a median of 13.3-years-old (8.3, 16.3), significantly older than patients with normal AST and ALT ($p \leq 0.001$; Table 1). In patients who had any elevation in transaminases, 67 (66%) were non-Hispanic and in those with grade 3–4 transaminase elevation, 6 (43%) were non-Hispanic. Both those with any transaminase elevation and those with highly elevated transaminases had significantly fewer non-Hispanic patients compared to those without transaminase elevations, $p = 0.04$ and $p = 0.01$, respectively (Table 1). There were no significant differences in sex, race, presence of a high-risk condition, or duration of remdesivir therapy with regards to any elevation of transaminases above the ULN nor with highly elevated transaminases (≥ 5x ULN) compared to patients without those elevations.

Associations of patient characteristics and transaminase elevations

Univariate analysis (Table 2) demonstrated that increasing age was associated with increased risk of any elevation of transaminases (OR 1.1 (95% CI, 1.1, 1.2); $p < 0.001$) and grade 3–4 transaminase elevation (OR 1.1 (95% CI, 1.0, 1.2); $p = 0.03$). Multivariable analyses were performed with outcomes of either "any transaminase elevation" or "grade 3–4 transaminase elevation," including all potential risk factors in the model. This showed that there were significant associations between age, respiratory disease severity, and any elevation of transaminases (Table 3). In addition to age and respiratory disease severity, Hispanic ethnicity was also significantly associated with grade 3–4 transaminase elevation (Table 3). Non-Hispanic ethnicity

Table 2 Univariate analysis of potential risk factors and transaminase elevation

	Any elevation of AST or ALT		Grade 3–4 elevation of AST or ALT	
	OR[a] (95% CI)	***p*-value[b]**	**OR[a] (95% CI)**	***p*-value[b]**
Age, continuous per year	**1.1 (1.1, 1.2)**	**<0.001**	**1.1 (1.0, 1.2)**	**0.03**
Ethnicity	**-**	**-**	**-**	-
Hispanic	**0.4 (0.2, 0.9)**	**0.03**	0.2 (0.1, 0.7)	**0.01**
Non-Hispanic				
Disease severity	**-**	**-**	**-**	-
Moderate	0.8 (0.4, 1.7)	0.63	1.0 (0.3, 4.2)	0.97
Severe	2.7 (0.8, 8.4)	0.09	3.1 (0.6, 15.2)	0.17
Critical				
Race	**-**	**-**	-	-
Black/African American	1.4 (0.7, 2.8)	0.30	1.3 (0.4, 4.7)	0.68
White/Caucasian	3.1 (0.3, 32.0)	0.34	1.5 (0.05, 48.3)	0.81
Other/Unknown				
Sex	-	-	-	-
Male	0.9 (0.5, 1.6)	0.74	1.2 (0.4, 3.7)	0.71
Female				
High-risk condition	-	-	-	-
Absent	1.8 (0.9, 3.8)	0.11	0.6 (0.2, 2.0)	0.40
Present				
Remdesivir duration, continuous per day	1.1 (0.9, 1.2)	0.34	1.0 (0.7, 1.2)	0.72

[a]OR = odds ratio

[b]p-values < 0.05 considered statistically significant, shown in bold

Table 3 Association of significant predictors and transaminase elevation in multivariate analysis

	Any elevation of AST or ALT		Grade 3–4 elevation of AST or ALT	
	aOR[a] (95% CI)	***p*-value[b]**	**aOR[a] (95% CI)**	***p*-value[b]**
Age, continuous per year	**1.1 (1.1, 1.2)**	**<0.001**	**1.1 (1.0, 1.3)**	**0.03**
Ethnicity	-	-	-	-
Hispanic	0.8 (0.3, 1.9)	0.56	**0.2 (0.05, 0.9)**	**0.04**
Non-Hispanic				
Disease severity	**-**	**-**	-	-
Moderate	0.8 (0.4, 1.9)	0.68	2.1 (0.4, 10.9)	0.37
Severe	**4.3 (1.1, 16.3)**	**0.03**	**9.8 (1.4, 69.4)**	**0.02**
Critical				
Race	**-**	**-**	-	-
Black/African American	1.5 (0.7, 3.4)	0.31	0.7 (0.2, 3.3)	0.67
White/Caucasian	6.5 (0.5, 81.3)	0.15	0.9 (0.02, 38.9)	0.95
Other/Unknown				
Sex	-	-	-	-
Male	1.2 (0.6, 2.4)	0.68	2.2 (0.6, 7.9)	0.25
Female				
High-risk condition	-	-	-	-
Absent	1.1 (0.4, 3.0)	0.80	0.7 (0.2, 3.2)	0.69
Present				
Remdesivir duration, continuous per day	1.0 (0.8, 1.2)	0.72	0.7 (0.5, 1.0)	0.08

[a]aOR = adjusted odds ratio

[b]p-values < 0.05 considered statistically significant, shown in bold

was strongly associated with protection against grade 3–4 transaminase elevation (aOR 0.2 (95% CI 0.05, 0.9); $p=0.04$). Older age showed higher risk of transaminase elevation. Critical respiratory disease severity, compared to moderate respiratory disease, had increased risk of any transaminase elevation (aOR 4.3 (95% CI, 1.1, 16.03); $p=0.03$) and was associated with grade 3–4 transaminase elevation (aOR 9.8 (95% CI, 1.4, 69.4); $p=0.02$). Critical respiratory disease severity compared to severe respiratory disease severity was associated with higher risk of any transaminase elevation (aOR 5.07 (95% CI 1.5, 16.9); $p<0.01$) and grade 3–4 transaminase elevation (aOR 4.61 (95% CI 1.06, 19.9); $p=0.04$) (data not shown).

Discussion

Our large cohort of pediatric patients, including patients aged < 12-months, developed limited and transient laboratory abnormalities, providing data to support the safety of remdesivir in children of all ages with acute COVID-19. In our cohort, few patients demonstrated peak creatinine or transaminase elevation after remdesivir initiation. However, nearly one-quarter (42 of 177 patients, 24%) of patients had transaminase elevation at baseline which closely matches previously reported estimates of approximately 25–31% elevation in transaminases at presentation [18–20]. Similarly, a high proportion of patients in our cohort demonstrated elevated peak creatinine prior to remdesivir initiation. These findings serve as an important reminder that, in addition to the anti-viral, transaminase and creatinine elevation can be related to the natural course of the viral illness as has been previously reported [20–24].

Data on the safety of remdesivir in children, including patients under 12 months, has previously been limited to a few small cohort studies. One study of 77 pediatric patients showed similar rates of transaminase elevation (60%), but more patients with grade 3–4 elevation (34%). However, that group had a higher median age of 14 years and included only those with severe COVID-19 related disease [8], both characteristics found to be risks for transaminase elevation in our study. In contrast, a study of 48 pediatric patients with a median age of 12.5 years and 94% with moderate or severe disease severity demonstrated no liver toxicity [9]. Similarly, our study demonstrated a favorable safety profile for remdesivir in a larger number of hospitalized children of all ages and respiratory disease severity.

Adult data suggest that up to 7% experience transaminase elevation after remdesivir initiation suggesting hepatic injury as a drug side effect [4, 7, 25]. In our cohort, we found a large portion of patients (24%) with transaminase elevation that occurred at baseline suggesting disease-related rather than drug-related effect. While transaminase elevation was common at baseline, elevations that did occur after remdesivir initiation were mostly mild (grade 1–2). For those that experienced significant transaminase elevation, these elevations were transient. Older age, Hispanic ethnicity, and critical disease severity were associated with the most severe transaminase elevation. Graff et al. reported that age extremes were associated with more severe disease [26] which would support the hypothesis that these transaminase elevations were more likely caused by the disease and not by the remdesivir treatment. Graff, et al. also reported that patients of Hispanic ethnicity had higher likelihood of admission and increased odds of requiring respiratory support [26], again suggesting that more severe disease perhaps led to more organ dysfunction including elevated transaminases in this population. Applying this clinically, our data perhaps suggest baseline transaminase evaluation should be measured prior to remdesivir initiation to assess disease-related elevations. It also supports the potential benefit of repeat lab monitoring in specific populations, including those of older age, Hispanic ethnicity, or those with critical disease severity as more significant transaminase elevation was associated in these populations.

Adult data regarding side effects of remdesivir suggest approximately 3–5% will experience creatinine elevation though this elevation was similar in control groups suggesting disease-related rather than drug-related effect [4, 25]. Previously published pediatric data suggested 18% of pediatric patients experienced grade 3–4 elevation of creatinine [8]. A more recent study saw no evidence of renal impairment related to remdesivir use [9]. In our cohort, when creatinine elevation occurred after remdesivir was initiated, it was infrequent (10/152, 7%), limited to those of older age, and transient in patients without underlying chronic kidney disease. This supports checking creatinine concentrations at baseline prior to initiating remdesivir use, especially in those patients with underlying renal disease.

There are limitations to this study. First, the data represent patients treated at a single institution, perhaps limiting generalizability. As use of remdesivir in hospitalized patients with COVID-19 was the accepted standard of care, a comparator cohort of COVID-19 positive patients that did not receive remdesivir was not available. Additionally, this was a retrospective review without standardization for lab monitoring during the timeframe studied, limiting the data points obtained for each patient and with the potential for bias with more labs obtained in sicker patients. The nature of the pandemic itself potentially interfered with our investigation due to changes in age-related drug approvals, evolving guidelines on treatment duration, and changes in disease presentation with different SARS-CoV-2 variants. We did not demonstrate an association between lab abnormalities and the duration of remdesivir therapy. This may be because the majority of our patients received a short course of anti-viral therapy, reflecting how this medication was used clinically. Further investigation with standardization of lab monitoring and duration of remdesivir therapy is required to definitively differentiate the effects of disease and drug exposure on these laboratory changes. Although we did demonstrate an association between laboratory abnormalities and overall medical co-morbidities, there was insufficient power to assess the association with individual co-morbidities.

Conclusions

In our study of hospitalized children of all ages with COVID-19 who were treated with remdesivir, most patients experienced only mild and transient transaminitis and normal creatinine concentrations. These data support the manufacturer's recommendation for baseline lab evaluation in all patients prior to starting remdesivir and suggest monitoring labs on therapy might only be necessary in COVID-19 positive patients with underlying renal disease or patients at increased risk of transaminitis, particularly those of older age, of Hispanic ethnicity, or with more severe disease.

Abbreviations

COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
FDA	Food and Drug Administration
EUA	Emergency Use Authorization
kg	Kilograms
AST	Aspartate transaminase
ALT	Alanine transaminase
EHR	Electronic health record
REDCap	Research Electronic Data Capture
ULN	Upper limit of normal
IQR	Interquartile range
OR	Odds ratio
aOR	Adjusted OR
CI	Confidence interval
MIS-C	Multisystem inflammatory syndrome in children

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09833-9.

Supplementary Material 1

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None.

Author contributions

BP: conceptualization, methodology, investigation, data curation, formal analysis, writing - original draft preparation, writing- review and editing, visualization. AH: conceptualization, supervision, formal analysis, writing - original draft preparation, writing – review and editing. AP: formal analysis, data curation, writing – review and editing. ML: formal analysis, data curation, writing – review and editing. PH: supervision, data curation, formal analysis, writing - original draft preparation, writing – review and editing. KR: methodology, data curation, writing – review and editing. MM: conceptualization, methodology, writing – review and editing. KG: Conceptualization, methodology, supervision, data curation, writing – review and editing.

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Data availability

Data is provided within the manuscript or supplementary information files. The dataset generated and analyzed during the current study is not publicly available as it contains protected health information, but the de-identified dataset is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The need for informed consent was waived by the Children's Wisconsin Human Research Protection Program Institutional Review Board because of the retrospective nature of the study.

Financial Disclosure Statement

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Consent for publication

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Competing interests

The authors declare no competing interests.

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