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Real-world evaluation of early remdesivir in high-risk COVID-19 outpatients during Omicron including BQ.1/BQ.1.1/XBB.1.5

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Abstract

Background A trial performed among unvaccinated, high-risk outpatients with COVID-19 during the delta period showed remdesivir reduced hospitalization. We used our real-world data platform to determine the effectiveness of remdesivir on reducing 28-day hospitalization among outpatients with mild-moderate COVID-19 during an Omicron period including BQ.1/BQ.1.1/XBB.1.5.

Methods We did a propensity-matched, retrospective cohort study of non-hospitalized adults with SARS-CoV-2 infection between April 7, 2022, and February 7, 2023. Electronic healthcare record data from a large health system in Colorado were linked to statewide vaccination and mortality data. We included patients with a positive SARS-CoV-2 test or outpatient remdesivir administration. Exclusion criteria were other SARS-CoV-2 treatments or positive SARS-CoV-2 test more than seven days before remdesivir. The primary outcome was all-cause hospitalization up to day 28. Secondary outcomes included 28-day COVID-related hospitalization and 28-day all-cause mortality.

Results Among 29,270 patients with SARS-CoV-2 infection, 1,252 remdesivir-treated patients were matched to 2,499 untreated patients. Remdesivir was associated with lower 28-day all-cause hospitalization (1.3% vs. 3.3%, adjusted hazard ratio (aHR) 0.39 [95% CI 0.23–0.67], $p < 0.001$) than no treatment. All-cause mortality at 28 days was numerically lower among remdesivir-treated patients (0.1% vs. 0.4%; aOR 0.32 [95% CI 0.03–1.40]). Similar benefit of RDV treatment on 28-day all-cause hospitalization was observed across Omicron periods, aOR (95% CI): BA.2/BA2.12.1 (0.77[0.19–2.41]), BA.4/5 (0.50[95% CI 0.50–1.01]), BQ.1/BQ.1.1/XBB.1.5 (0.21[95% CI 0.08–0.57].

Conclusion Among outpatients with SARS-CoV-2 during recent Omicron surges, remdesivir was associated with lower hospitalization than no treatment, supporting current National Institutes of Health Guidelines.

Keywords COVID-19, Remdesivir, Outpatient, Omicron variant, SARS-CoV-2, Nonhospitalized, Veklury

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Background

Remdesivir (Veklury, GS-5734) is an intravenous antiviral that initially received U.S. Food and Drug Administration (FDA) approval as a 5–10 day course for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized patients [1, 2]. The PINETREE trial, targeted unvaccinated, high-risk, nonhospitalized patients within 7 days of symptom onset before the emergence of Delta and Omicron variants. The abbreviated 3-day course of remdesivir reduced the risk of hospitalization or death by 87% compared to placebo [3]. Based on these data, in January 2021, the FDA expanded the indication of remdesivir to include nonhospitalized, high-risk patients with mild-moderate COVID-19.

As SARS-COV-2 Omicron sublineages emerged with mutations rendering available neutralizing monoclonal antibody products inactive, antivirals have become the standard of care for high-risk ambulatory patients [4, 5]. Although oral nirmatrelvir-ritonavir remains a first-line therapy, use is limited by drug-drug interactions and selected comorbid conditions [6]. Remdesivir has become the primary alternate therapeutic option for many high-risk patients otherwise ineligible for nirmatrelvir-ritonavir [4, 7]. However, there is a lack of evidence on the impact of remdesivir on the outcomes of nonhospitalized patients in the era of the Omicron with high COVID-19 vaccination rates and population seroprevalence. We used our real-world data platform to evaluate the effectiveness of remdesivir when given to outpatients with early symptomatic COVID-19 during a SARS-CoV-2 Omicron predominant period including BQ.1/BQ.1.1/XBB.1.5.

Methods

Study design and participants

In this study, we employed a propensity-matched, observational cohort design to generate real-world evidence using previously described methods [8]. This study conforms to STROBE reporting (Supplemental 1). This study was a multi-centre collaboration between the University of Colorado, UCHealth, and the Colorado Department of Public Health and Environment. The Colorado Multiple Institutional Review Board approved the study with a waiver of informed consent. UCHealth is Colorado's most extensive health system, with 13 hospitals, more than 141,000 annual hospital admissions, numerous ambulatory sites, and affiliated pharmacies. Data were obtained from the electronic health record (EHR; Epic, Verona, WI) via the enterprise data warehouse, Health Data Compass. Vaccination records were obtained from the Colorado Comprehensive Immunization Information System, and mortality data from Colorado Vital Records. Prior reports describe additional platform details [8, 9].

As pre-specified in the statistical analysis plan (Supplemental 2), the cohort was comprised of adult patients with either EHR documentation of laboratory-confirmed SARS-CoV-2 infection (either polymerase chain reaction or antigen) or at least one outpatient remdesivir administration (not including emergency departments [ED] or observation units). The index date was defined as either the positive SARS-CoV-2 test date or, if a SARS-CoV-2 test result was unavailable, imputed as a random sample from the observed distribution of length of days between the positive test and remdesivir treatment date. We included patients with an index date between April 7, 2022, and February 7, 2023, corresponding with the pandemic period in which available anti-SARS-CoV-2 monoclonal antibodies were limited (Bebtelovimab) or ineffective (Sotrovimab) against dominant circulating Omicron variants (beginning with BA.4 and BA.5), necessitating use of remdesivir.

On January 21, 2022, the FDA expanded approval for a three-day course of remdesivir nonhospitalized patients with risk factors for severe disease with positive SARS-CoV-2 test within seven days of symptom onset. The dosing was 200 mg intravenously on day one, followed by 100 mg on days two and three. Shared decision-making by patients and clinicians regarding antiviral therapy generally aligned with the National Institutes of Health guidelines, which recommended remdesivir for patients with risk factors for severe COVID-19 and unable to take nirmatrelvir-ritonavir [4]. We did not exclude patients who lacked a EHR documented EUA-qualifying comorbidity, as eligibility criteria were not consistently available.

We excluded patients with (1) an order or administration of other available antiviral treatment, such as nirmatrelvir-ritonavir, molnupiravir or a neutralizing monoclonal antibody (bebtelovimab, sotrovimab, or tixagevimab/cilgavimab) within 10 days of index date (2) SARS-CoV-2 positive test during hospital admission or being in the hospital at the time of remdesivir treatment, or (3) a positive SARS-CoV-2 test more than ten days prior to the remdesivir medication order date (Supplemental Fig. 1). Given the extensive use of home self-testing during the study, we retained patients who were hospitalized or died later the same day as their observed SARS-CoV-2 positive test or remdesivir administration date. As a positive SARS-CoV-2 test was required for remdesivir administration, we did not exclude treated patients without documentation of a positive test and imputed an index SARS-CoV-2 test date. For both groups, we assumed that testing occurred at home or outside the health system.

Variable definitions

Hospitalization was defined as any inpatient or observation encounter documented in the EHR. We selected the first hospitalization that occurred the same day, or any day after, a SARS-CoV-2 positive test for untreated patients or after the order date for remdesivir for treated patients. ED visits were defined as any visit to the ED, with or without an associated inpatient or observation encounter. For remdesivir -treated patients, we selected the first ED visit that occurred at least one day after the medication administration date, given that remdesivir can be ordered from the ED for initiation in an ambulatory setting and should not be considered a treatment failure. Vaccination status was categorized by the number of vaccinations (0, 1, 2, or ≥3) administered before the index date. Comorbidity data for obesity, hypertension, cardiovascular disease, diabetes mellitus, pulmonary disease, and liver disease were derived from billing code data included in the Charlson and Elixhauser Comorbidity Indices. The number of comorbid conditions was calculated as the sum of these specific conditions, except for obesity and immunocompromised status, which were included separately. Immunocompromised status was defined as binary variable as well as a three-level variable (none, mild, moderate-severe) using definitions reported previously [8]. Based on Colorado genomic surveillance data (Supplemental Fig. 2) we categorized patients into three Omicron subvariant periods by index date: BA2/2.12 (March 26, 2022 – June 18, 2022), BA.4/BA.5 (June 19, 2022 – November 12, 2022), BQ.1/BQ.1.1/XBB.1.5 (November 13, 2022 – February 07, 2023).

Outcomes

The primary outcome was all-cause hospitalization within 28-days of the index date. A key secondary outcome was COVID-19-related 28-day hospitalization defined as any of the following: COVID-19 ICD-10 code (U07.1, J12.82, M35.81, Z20.822, M35.89), or use of any supplemental oxygen. Other secondary outcomes included 28-day all-cause mortality and 28-day all-cause ED visits.

Statistical analysis

To identify a remdesivir-treated group and a contemporaneous control group balanced on potentially measured confounding variables, we developed a propensity model using logistic regression, with remdesivir treatment as the dependent variable and the following covariates: age (18–44, 45–64, ≥65), sex, race/ethnicity (Non-Hispanic White, Hispanic, Non-Hispanic Black, Other), insurance status (private/commercial, medicare, medicaid, none/uninsured, other/unknown), obesity status, a count of other comorbid conditions (besides immunocompromised status and obesity, defined below), number of vaccinations, and categorical week of SARS-CoV-2 positive test date.

We then used the propensity score to perform nearest neighbor propensity matching with a caliper of 0.2, with a target control-to-treatment ratio of 2:1, and a standardized mean difference threshold of 0.1 [10]. We removed 10 remdesivir-treated patients and 2,449 untreated patients due to missing covariate data (Supplemental Table 1). All remdesivir patients were successfully matched with at least one untreated patient (Supplemental Fig. 2).

The primary analysis used a survival analysis conducted using a Cox Proportional Hazards Model in the propensity matched cohort to assess the association of RDV treatment with 28-day hospitalization. In the main analysis we set the start date to be the treatment date for patients that were treated and the COVID-19 positive test date for untreated patients. Additional analyses used Firth's Bias-reduced logistic regression models in the propensity-matched cohort to assess the association between treatment and 28-day hospitalization, 28-day mortality, and 28-day ED visits. Firth's logistic regression (logistf v1.24) addresses estimation issues related to low event rates and complete separation [11–13]. Logistic regression was used after matching to mitigate residual balance and enhance estimate precision [14]. All models were adjusted for age, sex, race/ethnicity, insurance status, obesity status, immunocompromised status, number of comorbid conditions, number of vaccinations, and Omicron subvariant period (BA.2/2.12.1, BA.4/5, BQ.1/BA1.1/XBB.1.5).

We estimated adjusted treatment effects for eight prespecified subgroups of interest by fitting interaction models adjusted for all variables of interest. Subgroups of interest included binary age (<65 vs. ≥65), binary obesity status, binary and three-level immunocompromised status, binary number of comorbidities (0–1 vs. ≥2), binary and three-level vaccination status (0 vs. 1–2 vs. ≥3), and Omicron subvariant period (BA.2/2.12.1, BA.4/5, BQ.1/BA1.1/XBB.1.5). As described previously, we performed several sensitivity analyses to test assumptions related to definitions above [8]. These included limiting the dataset to only those patients with documentation of EUA-qualifying comorbid conditions, changing the imputed index date to 10 days before the first remdesivir dose for patients without a documented SARS-CoV-2 test, and excluding patients admitted to the hospital the same day as their positive test. We investigated these cases in separate sensitivity analyses with revised propensity matching and final models. Statistical analyses were performed using R (v3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

Additional sensitivity analyses were conducted to specifically address the potential for immortal time bias.

In the first analysis, we set the index date as the treatment date for patients that were treated and the COVID positive date for untreated patients, then fit a Cox Proportional Hazard Model. In a second analysis, we set the start date to be the treatment date for patients who were treated, while the covid positive date was used for untreated patients with interval-censored time to follow up. We then performed a Cox proportional hazards model. As a final sensitivity analysis, we conducted a time distribution matching analysis, which simulates treatment timing for untreated patients. We randomly assign each untreated patient a "treatment date" by sampling time-to-treatment data from treated patients. We then remove untreated patients whose hospitalization or death occurred before this new start date. For all patients, we recalculate follow-up time from the (actual or simulated) treatment date to the first post-COVID hospitalization and reassign the 28-day hospitalization flag accordingly. Finally, we repeat the propensity matching and modeling process used in the main analysis. This process was repeated 100 times to confirm the consistency of conclusions with resampling.

Results

We screened a total of 26,229 patients for inclusion (Supplemental Fig. 2). After exclusions, 17,632 patients were available for analysis: 1,289 remdesivir-treated patients and 16,343 untreated patients. See Supplementary Table 2 for clinical characteristics of the full cohort. After propensity matching, the final cohort (n=3,751) comprised 1,252 remdesivir-treated patients and 2,499 untreated controls (ratio 1:1.98). After matching, patients in the treatment and control groups were well-balanced on demographic and clinical characteristics (Table 1, Supplemental Table 3). Remdesivir-treated subjects demonstrated characteristics consistent with a high risk for progression to severe COVID-19. A large proportion were ≥65 years of age (47.4%, n=594/1,252), many had two or more comorbid conditions (50.0%, n=626/1,252), and a substantial proportion were immunocompromised (30.2%, n=379/1,252). Most remdesivir treated-patients had at least one COVID-19 vaccination (70.8%, n=887/1,252). The majority of remdesivir-treated patients received all three doses of remdesivir (94.8%, n=1187/1252), and uncommonly received only one (2.6%, n=32/1252 [2.6%]) or two doses (2.6%, n=33/1252).

In the primary analysis (Table 2, Supplemental Table 4), patients receiving remdesivir exhibited a 61% reduction in the risk of 28-day all-cause hospitalization compared to those who did not receive treatment (aHR 0.39 [95% CI 0.23–0.67], p<0.001). The odds of COVID-related 28-day hospitalization were similarly reduced by 62% in the remdesivir-treated cohort compared to untreated (aOR=0.37 [95% CI 0.20–0.63]). The primary outcome was robust to all prespecified sensitivity analyses (Table 3). In addition, the result was similar in the logistic regression analysis (aOR 0.38 [95% CI 0.22–0.64], p<0.001). In the time distribution matching analysis, the effect of remdesivir on 28-day hospitalization, although attenuated, remained consistent with previous analyses (HR 0.59 [95% CI 0.33–1.05], p=0.07). The effect of race was collapsed, likely due to the small sample size (Supplementary Table 10). The results of the time-matching approach appear consistent in each resampling, as observed in the distribution of treatment estimates and P-values (Supplemental Fig. 3).

For the remdesivir-treated group, the odds of 28-day ED visits were increased by 18%, but this was not statistically significant (aOR=1.18 [95% CI 0.90–1.54]). The odds of 28-day all-cause mortality was 68% lower, but this was not statistically significant given the small number of deaths (aOR=0.32 95% CI [0.03–1.40]). In the exploratory analysis of patients who were hospitalized (n=98), 25% (n=4/16) in the remdesivir cohort versus 17.1% (n=14/82) in the untreated cohort were admitted to an ICU; mean (standardized deviation [SD]) length of ICU stay was 3.3 (2.2) days in the remdesivir cohort versus 5.0 (4.0) days in the untreated group.

In prespecified subgroup analyses (Fig. 1), remdesivir was associated with greater treatment effect in patients 65 years or older (OR 0.22 [95% CI 0.1–0.49]) than patients younger than 65 years (OR 0.76 [95% CI: 0.35–1.6], p for interaction=0.04) Remdesivir was associated with similar treatment effect in those with categorized with any immunocompromised status (OR 0.31 [95% CI 0.14–0.66]) and those without immunocompromise (OR 0.51 [95% CI 0.23–0.99], p for interaction=0.47). Notably, remdesivir was associated with benefit in both patients with no documented vaccination (OR 0.27 [95% CI 0.05–0.85]) and patients who received three or more doses (OR 0.33 [95% CI 0.16–0.68], p for interaction=0.37) across all COVID-19 vaccination strata). Further, remdesivir was associated with similar benefit on 28-day all-cause hospitalization across Omicron Subvariant periods – BA.2/BA2.12.1 (OR 0.77 [95% CI 0.19–2.41]), BA.4/5 (OR 0.50 [95% CI 0.50–1.01]), BQ.1/BQ.1.1/XBB.1.5 (OR 0.21 [95% CI 0.08–0.57], p for interaction=0.38).

Discussion

During a SARS-COV-2 Omicron variant period from BA.2 through XBB.1.5 in Colorado, including when SARS-COV-2 monoclonal antibodies were unavailable, treatment of nonhospitalized patients with remdesivir was associated with a 61% relative lower risk of all-cause hospitalization. The effect of treatment with remdesivir was consistent across age, comorbidities, vaccination status, and Omicron subvariant period, including during recent surges of BQ.1/BQ.1.1/XBB.1.5. Our

Table 1 Baseline characteristics by remdesivir treatment status for primary matched cohort

Variable	Remdesivir (*n* = 1,252)	Untreated (*n* = 2,499)	Overall (*n* = 3,751)
Age, No. (%), y			
18–44 years	233 (18.6%)	432 (17.3%)	665 (17.7%)
45–64 years	425 (33.9%)	871 (34.9%)	1296 (34.6%)
≥ 65 years	594 (47.4%)	1196 (47.9%)	1790 (47.7%)
Female Sex, No. (%)	697 (55.7%)	1416 (56.7%)	2113 (56.3%)
Race/Ethnicity, No. (%)			
Non-Hispanic White	1072 (85.6%)	2171 (86.9%)	3243 (86.5%)
Hispanic	106 (8.5%)	210 (8.4%)	316 (8.4%)
Non-Hispanic Black	40 (3.2%)	67 (2.7%)	107 (2.9%)
Other	34 (2.7%)	51 (2.0%)	85 (2.3%)
Insurance Status, No. (%)			
Medicaid	53 (4.2%)	118 (4.7%)	171 (4.6%)
Medicare	579 (46.2%)	1159 (46.4%)	1738 (46.3%)
Other (None/Uninsured/Unknown)	37 (3.0%)	61 (2.4%)	98 (2.6%)
Private/Commercial	583 (46.6%)	1161 (46.5%)	1744 (46.5%)
Immunocompromised Status, No. (%)			
None	873 (69.7%)	1,788 (71.5%)	2,661 (70.9%)
Mild	171 (13.7%)	324 (13.0%)	495 (13.2%)
Moderate/Severe	208 (16.6%)	387 (15.5%)	595 (15.9%)
Obesity Status, No. (%)	434 (34.7%)	858 (34.3%)	1292 (34.4%)
Number of Other Comorbid Conditions, No. (%)			
None	298 (23.8%)	616 (24.6%)	914 (24.4%)
One	328 (26.2%)	696 (27.9%)	1024 (27.3%)
Two or more	626 (50.0%)	1187 (47.5%)	1813 (48.3%)
Diabetes, No. (%)	272 (21.7%)	514 (20.6%)	786 (21.0%)
Cardiovascular Disease, No. (%)	331 (26.4%)	616 (24.6%)	947 (25.2%)
Pulmonary Disease, No. (%)	460 (36.7%)	849 (34.0%)	1309 (34.9%)
Renal Disease, No. (%)	182 (14.5%)	328 (13.1%)	510 (13.6%)
Hypertension, No. (%)	683 (54.6%)	1352 (54.1%)	2035 (54.3%)
Liver Disease, No. (%)			
None	1,093 (87.3%)	2,207 (88.3%)	3,300 (88.0%)
Mild	141 (11.3%)	278 (11.1%)	419 (11.2%)
Severe	18 (1.4%)	14 (0.6%)	32 (0.9%)
Number of prior COVID-19 vaccinations, No. (%)			
0	183 (14.6%)	412 (16.5%)	595 (15.9%)
1–2	182 (14.5%)	343 (13.7%)	525 (14.0%)
≥ 3	887 (70.8%)	1744 (69.8%)	2631 (70.1%)
Omicron Subvariant Period, No. (%)			
BA.2/BA.2.12	324 (25.9%)	689 (27.6%)	1,013 (27.0%)
BA.4/BA.5	660 (52.7%)	1,348 (53.9%)	2,008 (53.5%)
BQ.1/BQ.1.1/XBB.1.5	268 (21.4%)	462 (18.5%)	1,292 (34.4%)

Table 2 Primary and secondary outcomes for remdesivir treatment for primary matched cohort

Outcome	No. (%)		Adjusted Odds or Hazard Ratio (95% CI)	*P* value
	Remdesivir (*n* = 1,252)	Untreated (*n* = 2,499)		
All-cause 28-day hospitalization	16 (1.3%)	82 (3.3%)	0.38 (0.22–0.64)[a]	< 0.001
COVID-related 28-day hospitalization	14 (1.1%)	76 (3.0%)	0.37 (0.20–0.63)	< 0.001
All-cause 28-day ED visit	95 (7.6%)	162 (6.5%)	1.18 (0.90–1.54)	0.23
All-cause 28-day mortality	1 (0.1%)	10 (0.4%)	0.32 (0.03–1.40)	0.15

* All models adjusted for age, sex, race/ethnicity, obesity, immunocompromised status, number of comorbidities, insurance status, vaccination status, and subvariant period

a. Adjusted Hazard Ratio

Table 3 Primary and sensitivity analyses for all-cause hospitalization at 28 days

Outcome	No./total (%)		Adjusted Odds Ratio (95% CI)	*P* value
	Remdesivir	Untreated		
Primary Matched Cohort	16/1252 (1.3%)	82/2,499 (3.3%)	0.38 (0.22–0.64)	< 0.001
Emergency use authorization-qualifying condition only	16/1,261 (1.3%)	90 /3,761 (3.6%)	0.35 (0.20–0.58)	< 0.001
SARS-CoV-2 test date imputation with fixed 7 days	18/1,310 (1.4%)	94/2,587 (3.6%)	0.35 (0.20–0.57)	< 0.001
Cohort excluding same day hospitalization	15/1261 (1.2%)	40/1261 (3.2%)	0.43 (0.22–0.77)	0.004

All sensitivity analyses were fit using Firth's bias-reducing logistic regression, with 28-day all-cause hospitalization as the outcome, and were adjusted for all covariates in the primary analysis

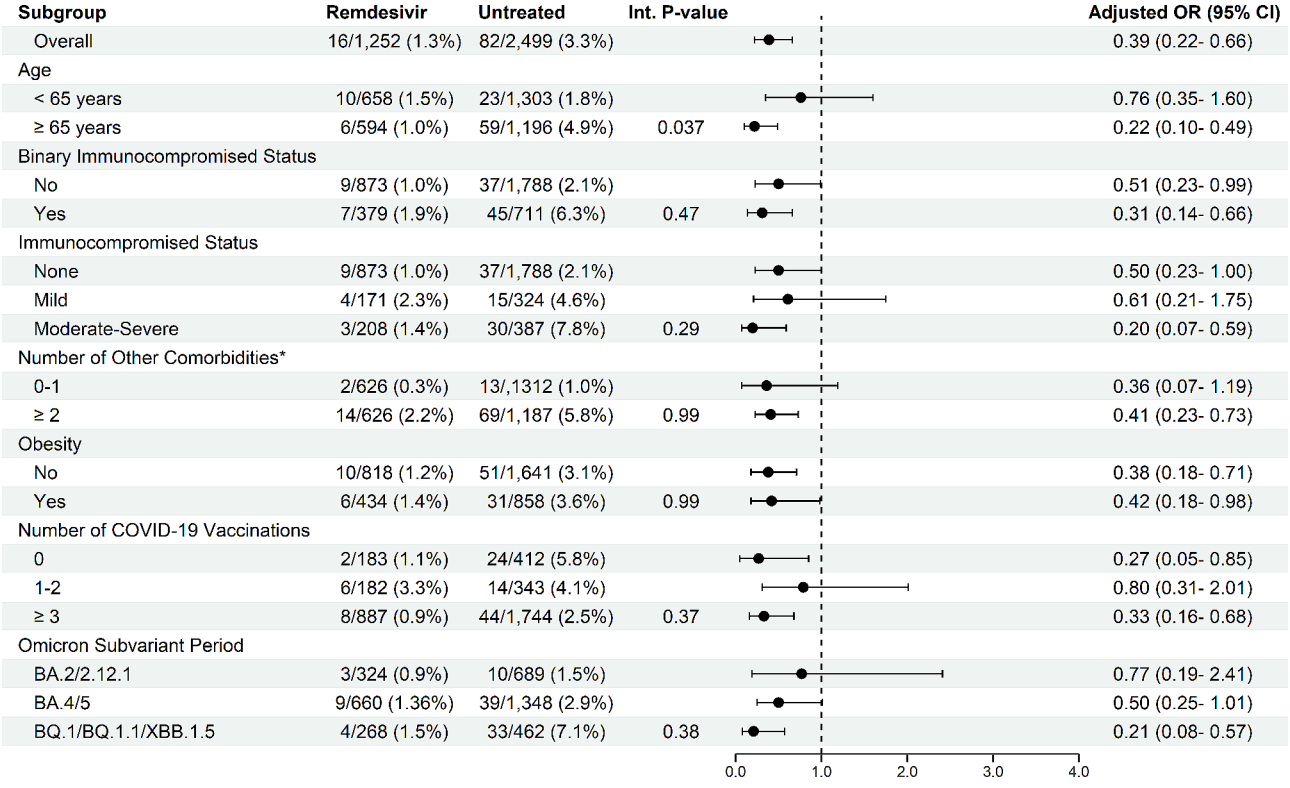

Fig. 1 Forest plot for subgroup analysis of outpatients infected with Omicron. The primary outcome for all subgroup analyses was 28-day all-cause hospitalization. All subgroup models were adjusted for all variables in the primary analysis. Raw counts and proportions are presented, along with the adjusted OR (95% CI) for the treatment effect in the subgroup of interest. OR = odds ratio. Binary Immunocompromised status includes any IC status

findings closely mirror that of the PINETREE trial, in which unvaccinated patients that received remdesivir had an 87% lower risk of hospitalization or death than placebo. Further, the effect size in this study is similar to that observed in our previous evaluation of nirmatrelvir-ritonavir during an overlapping Omicron period (BA.2./BA2.12.1, BA.4/BA.5) [8]. Our findings suggest that early remdesivir is associated with lower hospitalization in vaccinated populations and is a reasonable option for patients who cannot receive nirmatrelvir-ritonavir.

Data regarding the effectiveness of remdesivir among outpatients with mild-moderate COVID-19 remain limited. Piccicacco et al. conducted a small retrospective cohort study of nonhospitalized patients during the Omicron B.1.1.529 period comparing those that received a 3-day course of remdesivir to randomly selected high-risk outpatients that declined remdesivir or sotrovimab. Most of the 82 remdesivir -treated patients were immunocompromised, and most were vaccinated (83%) [15]. Treatment with remdesivir was associated with reduced risk of COVID-19-related hospitalization or ED visit within 29 days compared to control (11% vs. 23%, OR [95% CI]: 0.41 [0.17–0.95]). Other reports have also shown remdesivir treatment as associated with similar

benefits in reduction of hospitalization as other therapeutics including nirmatrelvir/ritonavir and sotrovimab [16, 17]. Our study extends these findings with a larger sample size during an Omicron period, including BA2/BA2.12, BA.4/BA.5, and BQ.1/BQ.1.1/XBB.1.5.

In November of 2022, the emergence of Omicron BQ and XBB variants rendered bebtelovimab, the available neutralizing monoclonal antibody, inactive, which left oral antivirals and remdesivir as the sole early therapeutic options for outpatients with COVID-19. Oral antivirals are advantageous in terms of route of administration, with the lack of need for parenteral administration by a healthcare professional and subsequent coordination at a healthcare facility. Drug-drug interactions with nirmatrelvir-ritonavir, comorbidities (e.g. severe renal and liver disease), and the limited effectiveness of molnupiravir preempt the use of these antivirals in many patients [6, 18]. The administration of intravenous remdesivir to nonhospitalized adults at scale presents a substantial logistical challenge for health systems. Compared to neutralizing monoclonal antibodies requiring a single infusion, remdesivir requires multiple infusions over three days – increasing the healthcare resources and patient burden for each treatment course. Our data suggest that most patients (~95%) can complete a 3-day course. Additional data are needed to support the generalizability of this adherence rate. Oral remdesivir analogues may ultimately limit the future need for intravenous administration for nonhospitalized patients [19]. ' [20].

This study has several limitations that should be considered. First, as our study is observational, we cannot exclude the possibility of residual confounding. Second, symptom duration was unavailable in our data, so we cannot determine whether all patients were treated within seven days of onset. Third, given the use of a single health system electronic health record, misclassification of treatment status and outcomes may have occurred due to events outside of the health system. However, the implementation of remdesivir was limited across Colorado due to logistical challenges, and our statewide mortality data is robust. The limited symptom data introduces the potential for immortal time and biases related to left truncation. We used several methods and sensitivity analyses to investigate the potential for these biases and were reassured by consistency across analyses.

In conclusion, treatment with remdesivir was associated with reduced odds of 28-day all-cause hospitalization during Omicron variant periods, including BQ.1/BQ.1.1/XBB.1.5 in Colorado. These data support current NIH guideline recommendations for utilization of remdesivir as first-line treatment in those unable to take nirmatrelvir-ritonavir.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09708-z.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
AAG conceived and obtained funding for the study. KCM, VK, NRA, LEB, NEC, and AAG designed the study. LEB and NEC analysed the data. VK, LEB, TDB, NEC, DAM, and SR accessed and verified the data. KCM and VK drafted the original version of the manuscript. All authors had full access to the data, reviewed the manuscript, contributed to data interpretation, approved the final version and accept responsibility to submit for publication.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Colorado Multiple Institutional Review Board (COMIRB). The requirement for informed consent was waived by COMIRB provided a lack of feasibility to retrospectively consent patients.

Consent for publication
Not applicable.

Consent for publication
Not applicable.

Conflict of interest
KCM reports honoraria for serving on the speakers bureau for Melinta Therapeutics, Innoviva Specialty Therapeutics, and Shionogi Inc. NRA reports grants from the US National Institutes of Health (NIH), during the conduct of the study. TDB reports grants from the NCATS, during the conduct of the study, and grants from the NICHD and NHLBI, outside of the submitted work. NEC reports grants from the US NIH, during the conduct of the study. AAG reports grants from the US NIH during the conduct of the study, grants from the US Centers for Disease Control, the US Department of Defense, AbbVie, and Faron Pharmaceuticals, and participation on an NIH data safety monitoring board, outside of the submitted work. All other authors declare no competing interests. All other authors report no conflicts of interest.

Competing interests
The authors declare no competing interests.

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