


# Disease-Specific Factors Associated with Readmissions or Mortality After Hospital Discharge in COVID-19 Patients: a Retrospective Cohort Study



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**BACKGROUND:** Understanding the implications of disease-specific factors beyond baseline patient characteristics for coronavirus disease 2019 (COVID-19) may allow for identification of indicators for safe hospital discharge.

**OBJECTIVE:** Assess whether disease-specific factors are associated with adverse events post-discharge using a data-driven approach.

**DESIGN:** Retrospective cohort study.

**SETTING:** Fifteen medical centers within Kaiser Permanente Southern California.

**PARTICIPANTS:** Adult patients ( $n=3508$ ) discharged alive following hospitalization for COVID-19 between 05/01/2020 and 09/30/2020.

**INTERVENTIONS:** None.

**MAIN MEASURES:** Adverse events defined as all-cause readmission or mortality within 14 days of discharge. Least absolute shrinkage and selection operator (LASSO) was used for variable selection and logistic regression was performed to estimate odds ratio (OR) and 95% confidence interval (CI).

**KEY RESULTS:** Four variables including age, Elixhauser index, treatment with remdesivir, and symptom duration at discharge were selected by LASSO. Treatment with remdesivir was inversely associated with adverse events (OR: 0.46 [95%CI: 0.36–0.61]), while symptom duration  $\leq 10$  days was associated with adverse events (OR: 2.27 [95%CI: 1.79–2.87]) in addition to age (OR: 1.02 [95%CI: 1.01–1.03]) and Elixhauser index (OR: 1.15 [95%CI: 1.11–1.20]). A significant interaction between remdesivir and symptom duration was further observed ( $p=0.01$ ). The association of remdesivir was stronger among those with symptom duration  $\leq 10$  days vs  $>10$  days at discharge (OR: 0.30 [95%CI: 0.19–0.47] vs 0.62 [95%CI: 0.44–0.87]), while the association of symptom duration  $\leq 10$  days at discharge was weaker among those treated with remdesivir vs those not treated (OR: 1.31 [95%CI: 0.79–2.17] vs 2.71 [95%CI 2.05–3.59]).

**CONCLUSIONS:** Disease-specific factors including treatment with remdesivir, symptom duration, and their interplay may help guide clinical decision making at time of discharge.

**KEY WORDS:** readmission; COVID-19; remdesivir.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel disease with a prolonged course which may have implications beyond the initial hospitalization.<sup>1,2</sup> There has been growing interest in characterizing the post-discharge course of COVID-19 to better understand its disease burden.<sup>3,4</sup> Recent studies have reported relatively low rates of readmissions predominantly from respiratory complaints early in the post-discharge period.<sup>3,5–7</sup> Studies have also identified increased age and comorbidities to be associated with readmissions.<sup>3,4,7</sup>

Despite growing understanding of post-discharge outcomes and risk factors for readmissions following hospitalization, the optimal timing for discharging patients hospitalized with COVID-19 remains uncertain. Many identified risk factors, such as age and comorbidities, are fixed and not actionable for healthcare providers. There is limited understanding of how disease-specific factors, such as treatments received and peri-discharge clinical parameters, affect post-discharge outcomes.<sup>8</sup> Moreover, the implications of COVID-19 therapies beyond the acute course are not well described and there is even some controversy over the efficacy of remdesivir in the treatment of COVID-19.<sup>6,9–11</sup> A few other studies have explored incomplete aspects of this topic and have been limited by size and/or single-center experiences with conflicting results.<sup>6,8,9,12</sup>

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Understanding how COVID-19 therapies and peri-discharge clinical parameters may affect the disease course beyond the initial hospitalization can potentially help identify clinical indicators for safe hospital discharge and guide clinical decision making. To address this knowledge gap, we used a data-driven approach to assess whether disease-specific factors during the index COVID-19 hospitalization are associated with 14-day all cause readmission or mortality.

## METHODS

### Study Setting and Data Sources

This is a retrospective cohort study involving 15 medical centers within Kaiser Permanente Southern California (KPSC). KPSC is an integrated health system providing comprehensive care to over 4.7 million racially/ethnically and socio-economically diverse members who reflect the general population in Southern California.<sup>13,14</sup> We selected May 2020 to begin our study period given this was the month emergency use authorization was granted for remdesivir in the USA and with it, some standardization of practice.<sup>15</sup>

KPSC has a comprehensive, integrated electronic health records (EHR) and claims data system which allows for complete data capture both within and outside the system. All variables including baseline sociodemographic, comorbidities, clinical, medications, and laboratory, and utilization data were extracted electronically unless otherwise stated. All data for this study were collected as part of routine clinical encounters in which healthcare providers determined the need for laboratory measurements, procedures, and medications.

### Study Population

Adult patients ( $\geq 18$  years of age) who were hospitalized for COVID-19 between 5/1/2020 and 9/30/2020 and discharged alive were included in the study. COVID-19 hospitalization was defined as an observation stay or inpatient admission with COVID-19 International Classification of Diseases (ICD) -10 code: U07.1 and a positive SARS-CoV-2 nucleic acid amplification test (NAAT) within 14 days prior to and up to 48 h after admission. The first COVID-19 hospitalization within the study period was defined as the index hospitalization; patients with a COVID-19 hospitalization prior to the study period were excluded from the study to avoid labeling a readmission as an index hospitalization. Patients discharged to hospice, against medical advice, or to another acute care hospital were excluded. Non-network, pregnant, and non-medical service patients were also excluded to minimize inclusion of patients with incomplete follow-up data or patients who were not primarily admitted for COVID-19. Our study was approved by the KPSC Institutional Review Board (IRB# 12558) and informed consent was waived.

### Disease-Specific Factors

Disease-specific factors reflected variables factored into discharge decisions based on the authors' experience, including therapies received and peri-discharge clinical parameters. Therapies of interest consisted of remdesivir and corticosteroids (dexamethasone, hydrocortisone, methylprednisolone, prednisone, or prednisolone in intravenous or enteral form), two evidence-based therapies for COVID-19 adopted into guidelines in the USA during the study period.<sup>16,17</sup>

Peri-discharge clinical parameters included symptom duration, discharge vitals, and laboratory trend. Categorizations of these variables were chosen for potential translational value for healthcare providers. Symptom duration at discharge was categorized as  $\leq 10$  days or  $>10$  days; symptom onset date was defined as day 1. Admission date was used as the symptom onset date for patients unable to be identified as symptomatic prior to hospitalization. Charts missing this data electronically were manually reviewed by one of the clinician investigators. Duration of observed afebrile ( $\leq 100.4$  °F) period at discharge was categorized as  $<24$  h, 24–48 h, 48–72 h, and  $\geq 72$  h; if never febrile, this period was categorized accordingly based on duration of hospitalization. The 10-day and 72-h cutoffs were chosen based on previous isolation discontinuation guidelines.<sup>18,19</sup> Last recorded values prior to discharge were used for oxygen requirement and oxygen saturation at discharge; oxygen requirement was categorized as room air, 1–2 L/min of oxygen, 3–4 L/min of oxygen, and  $\geq 5$  L/min. Oxygen saturation was categorized as normoxia ( $O_2$  saturation  $\geq 94\%$ ) or hypoxia ( $O_2$  saturation  $<94\%$ ). The 94% cutoff was chosen based on the definition of severe COVID-19 disease.<sup>20</sup> C-Reactive protein (CRP) trend was also considered. A decreased trend was defined as consecutively decreasing or normalizing values over the last three measurements prior to discharge. Normalization of CRP was defined as a value  $\leq 7.4$  mg/L, the reference range for normal values within KPSC laboratory. Three measurements were chosen to maximize consistency.

### Outcome

The primary composite outcome was all-cause readmission or mortality within 14 days from discharge. A readmission was defined as an observation stay or inpatient admission. A 14-day period was chosen to better reflect outcomes most likely related to COVID-19 and the index hospitalization given reports of early readmissions following hospitalization for COVID-19.<sup>3,6,7</sup>

### Co-variables

Baseline sociodemographic variables including age, sex, race, body mass index, and tobacco use were included, as well as missed appointments and prior hospitalizations within the year prior to index hospitalization.<sup>7,21</sup> The Elixhauser index and specific comorbidities identified as significant in prior studies

were extracted using ICD codes.<sup>3,22</sup> The Elixhauser index is a summative capture of the number of Elixhauser comorbidities present with a higher number indicative of more comorbidities.<sup>22</sup> We included it given its excellent performance in predicting both short- and long-term mortality and to account for any residual confounding beyond that of individual comorbidities previously identified.<sup>23</sup> Other potential therapeutics of unproven benefit at the time of the study period were also considered and included convalescent plasma, therapeutic anticoagulation, anakinra, and tocilizumab. Due to the limited use of tocilizumab during the study period, tocilizumab and anakinra were combined into one category labeled biologics. Clinical acuity variables including need for intensive care, length of stay, and highest oxygen requirement during hospitalization were also included. Finally, functional status within 24 h of discharge and discharge disposition were included.<sup>3,7,24</sup>

**Missing Data**

Incomplete data were assumed to be missing at random and multiple imputation was employed to avoid reducing the number of observations for the model. Missingness was highest for CRP trend (6.2%), followed by mobility status within 24 h of discharge (5.4%), and was <1% for the remaining missing variables (BMI, tobacco use, and oxygen requirement at discharge). The missing values were imputed with pooled results after 25 imputations.

**Statistical Analysis**

Baseline characteristics were presented descriptively. Continuous variables were presented as medians with interquartile ranges (IQR) and categorical variables were presented as frequencies and percentages (%).

In our primary analysis, we first performed least absolute shrinkage and selection operator (LASSO) for variable selection of all variables in Table 1 after multiple imputation for missing data. LASSO is a regularization technique that selects variables through removing variables considered potentially redundant or insignificant, thus optimizing model accuracy and interpretability. Group LASSO was also used to ensure that variables with multiple categories were treated as a single unit when undergoing selection, resulting in a parsimonious model retaining the most informative variables. Selected variables were then included in a multivariable logistic regression model to estimate the odds ratio (OR) and 95% confidence intervals (CI). Interaction between remdesivir and symptom duration was also assessed using a deviance test with a significance threshold of 0.05.

Two additional sensitivity analyses were then performed to assess the validity of our findings, in each case using LASSO as an initial variable screening step for a final logistic regression model. First, a complete case analysis excluding patients with missing data was performed. Subsequently, another analysis excluding patients who either required manual chart

**Table 1. Baseline Characteristics of Cohort**

Disease-specific factors	All patients (n=3508)*
Treatment with remdesivir	1580 (45%)
Treatment with corticosteroids	2411 (68.7%)
Symptom duration at discharge†	
≤10 days	1245 (35.5%)
>10 days	2263 (64.5%)
Duration of afebrile period at discharge	
<24 h	299 (8.5%)
≥24 and <48 h	585 (16.7%)
≥48 and <72 h	546 (15.6%)
≥72 h	2078 (59.2%)
Oxygen requirement at discharge‡	
No oxygen or room air	2087 (59.5%)
1–2 L/min	991 (28.3%)
3–4 L/min	361 (10.3%)
5+ L/min	56 (1.6%)
Oxygen saturation at discharge	
≥94%	2835 (80.8%)
<94%	673 (19.2%)
Decreasing C-reactive protein trend‡	1972 (56.2%)
Other baseline characteristics and co-variates	
Age	57 (46-68)
Female	1560 (44.5%)
Race	
White	478 (13.6%)
Black	259 (7.4%)
Hispanic	2407 (68.6%)
Asian	331 (9.4%)
Other	33 (1%)
Body mass index‡	30.4 (26.5-35.5)
Did not keep at least one appointment within prior year	2056 (58.6%)
Hospitalization within prior year	551 (15.7%)
Elixhauser	3 (2-5)
Diabetes	1481 (42.2%)
Hypertension	1129 (32.2%)
Congestive heart failure	529 (15.1%)
Chronic pulmonary disease	760 (21.7%)
Chronic kidney disease	511 (14.6%)
Smoking (ever)‡	1163 (33.2%)
Treatment with convalescent plasma	474 (13.5%)
Treatment with biologics including anakinra or tocilizumab	463 (13.2%)
Treatment with therapeutic anticoagulation	757 (21.6%)
Highest oxygen requirement	
Room air	674 (19.2%)
Supplemental oxygen	2353 (67.1%)
Non-invasive positive pressure ventilation/high-flow	360 (10.3%)
Mechanical ventilation	121 (3.5%)
Intensive care	241 (6.9%)
Length of stay	5 (3-8)
Functional status within 24 h of discharge‡	
Non-ambulatory	318 (9.1%)
Ambulatory with assistance	2113 (60.2%)
Ambulatory without assistance	889 (25.3%)
Discharge disposition	
Home	2433 (69.4%)
Home health	895 (25.5%)
Skilled nursing facility	180 (5.1%)

\*Data presented as median (interquartile range) or frequency (percentage)

†Obtained by manual chart review (n=369), defaulted to length of stay (n=249)

‡Missing data: oxygen requirement= 13, C-reactive protein= 219, body mass index = 8, smoking=16, functional status =188

review or for whom we were unable to identify as symptomatic prior to hospitalization was performed.

In a secondary analysis, an all-variable analysis of all variables in Table 1 including multiple imputation for missing data was performed to examine the relationships of other

disease-specific factors that may not have been included through LASSO or due to missingness. A sensitivity analysis was performed on the all-variable model by excluding those who were never febrile but hospitalized <72 h to avoid misclassification bias introduced by assuming similarity among these patients and those observed to be afebrile for <72 h.

All statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC).

## RESULTS

A cohort of 3508 patients who were discharged alive after an index COVID-19 hospitalization during the study period was identified, of which 342 (9.7%), 667 (19%), 1324 (37.7%), 703 (20%), and 472 (13.5%) patients were discharged in May, June, July, August, and September, respectively. The median age was 57 (IQR:46–68) years, 1560 (44.5%) patients were female, and most patients were Hispanic (68.6%). A total of 377 (10.8%) patients experienced a readmission or death within 14 days from discharge. Of the 377 adverse events, 360 (95.5%) were attributable to readmissions.

Of the cohort, 1580 (45%) patients were treated with remdesivir and 2411 (68.7%) patients were treated with corticosteroids. At discharge, 1245 (35.5%) patients had  $\leq 10$  days of symptoms and 673 (19.2%) patients were hypoxic ( $O_2 < 94\%$ ), while 2087 (59.5%), 991 (28.3%), 361 (10.3%), and 56 (1.6%) patients required room air, 1–2 L/min, 3–4 L/min, and  $\geq 5$  L/min, respectively, and 299 (8.5%), 585 (16.7%), 546 (15.6%), and 2078 (59.2%) patients were observed to be afebrile for <24 h, 24–48 h, 48–72 h, and  $\geq 72$  h, respectively. Additionally, 1972 (56.2%) patients had a decreasing CRP trend at discharge (Table 1).

In our primary analysis, four variables were selected by LASSO as being associated with the composite outcome of 14-day all-cause readmission or mortality, of which two were disease-specific factors: treatment with remdesivir (OR: 0.46 [95% CI: 0.36–0.61]) and symptom duration  $\leq 10$  days at discharge (OR: 2.27 [95% CI: 1.79–2.87]). The two other variables selected in the model included age (OR: 1.02 [95% CI: 1.01–1.03]) and Elixhauser index (OR: 1.15 [95% CI: 1.11–1.20]) (Table 2). Our two sensitivity analyses provided similar results other than the additional inclusion of congestive heart failure (OR: 1.40 [95% CI: 0.97–2.01]) in the sensitivity analysis excluding patients who either required manual chart

review or for whom we were unable to identify as symptomatic prior to hospitalization (Appendix Table 4).

There was a significant interaction between treatment with remdesivir and symptom duration ( $p = 0.01$ ). Among patients who received remdesivir, the OR for 14-day all-cause readmission or mortality was 0.30 (95% CI: 0.19–0.47) for those with symptom duration  $\leq 10$  days at discharge and 0.62 (95% CI: 0.44–0.87) for those with symptom duration  $> 10$  days at discharge. Among patients who had a symptom duration  $\leq 10$  days at discharge, the OR for 14-day all-cause readmission or mortality was 2.71 (95% CI: 2.05–3.59) for those who were not treated with remdesivir and 1.31 (95% CI: 0.79–2.17) for those who were treated with remdesivir (Table 3).

In our secondary analysis with an all-variable model, the estimates for remdesivir and symptom duration with 14-day all-cause readmission or mortality were also similar. We additionally observed a dose-dependent relationship between shorter afebrile duration (<24 h: OR: 4.30 [95% CI: 2.84–6.52]; 24–48 h: OR: 2.35 [95% CI: 1.64–3.36]; 48–72 h: OR: 1.40 [95% CI: 0.96–2.03]) and increased oxygen requirement (1–2 L/min: 1.08 [95% CI: 0.79–1.48]; 3–4 L/min: OR: 1.84 [95% CI: 1.21–2.81];  $\geq 5$  L/min: OR: 3.15 [95% CI: 1.42–6.97]) at discharge with adverse events. Oxygen saturation  $< 94\%$  at discharge was also associated with adverse events (OR: 1.43 [95% CI: 1.07–1.93]). Treatment with corticosteroids (OR: 1.30 [95% CI: 0.98–1.72]) and decreasing CRP trend (OR: 0.97 [95% CI: 0.76–1.25]) were not associated with 14-day all-cause readmission or mortality. (Appendix Table 5).

## DISCUSSION

In a large, diverse cohort of patients discharged alive following hospitalization for COVID-19, we found that treatment with remdesivir during the index hospitalization was associated with lower odds of 14-day all-cause readmission or mortality while symptom duration  $\leq 10$  days at discharge was associated with increased odds of these adverse events in addition to established factors like age and comorbidities. Treatment with remdesivir was most impactful among patients with symptom duration  $\leq 10$  days at discharge. Our study highlights the importance of select disease-specific factors

**Table 2. Odds Ratio for Adverse Events Within 14 Days Post-Discharge with LASSO Regression**

Disease-specific factors	Odds ratio (95% confidence interval)
Treatment with remdesivir vs no remdesivir	0.46 (0.36–0.61)
Symptom duration $\leq 10$ days vs $> 10$ days	2.27 (1.79–2.87)
Patient characteristics	
Age (years)	1.02 (1.01–1.03)
Elixhauser index	1.15 (1.11–1.20)

**Table 3. Odds Ratio for Adverse Events Within 14 Days Post-Discharge for Each Subgroup by Treatment with Remdesivir and Symptom Duration**

Subgroup	Odds ratio (95% confidence interval)*
Treatment with remdesivir vs no remdesivir	
Symptom duration $\leq 10$ days	0.30 (0.19–0.47)
Symptom duration $> 10$ days	0.62 (0.44–0.87)
Symptom duration $\leq 10$ days vs $> 10$ days	
No treatment with remdesivir	2.71 (2.05–3.59)
Treatment with remdesivir	1.31 (0.79–2.17)

\*Additionally adjusted for age (years) and Elixhauser index

and their potential value when discharging COVID-19 patients.

The effectiveness of remdesivir has been established in literature<sup>25</sup>; despite advances in novel therapies and despite milder diseases after vaccination and newer variants, remdesivir remains a first-line and readily accessible agent.<sup>26,27</sup> However, our finding regarding remdesivir adds new value by noting its association with reduced readmission or mortality after discharge. We believe this is plausible as earlier recovery via remdesivir may help prevent complications such as readmissions caused by continued disease.<sup>5-7,11,25</sup> Moreover, our finding is of practical significance as it allows providers to recognize that a patient, if treated with remdesivir prior, may have a more favorable post-discharge course even if still early in the disease course. Such information may be particularly useful in assessing for safe discharges when there is uncertainty.

The increased odds of adverse events with symptom duration  $\leq 10$  days were consistent with clinical expectations. Existing literature on the natural history of COVID-19 have noted clinical deterioration at around 8–12 days from symptom onset.<sup>28-30</sup> Thus, symptom duration exceeding 10 days for otherwise clinically stable patients likely indicates low risk for further decompensation. While we had to make assumptions on a small subset of patients (7.1%) that were unable to be identified as symptomatic prior to admission, a sensitivity analysis excluding this subset yielded similar results.

In our all-variable model, we additionally observed a dose-dependent relationship with duration of afebrile period and oxygen requirement at discharge and identified the cutoffs ( $< 48$  h and  $\geq 3$  L/min) where odds of adverse events were no longer statistically significant. Parra et al. have also reported 48 h of afebrile period to be of relevance, though others did not find any utility with discharge vitals.<sup>8,12</sup> Future studies on these variables and their utility are necessary.

At the same time, not all statistically significant variables in the all-variable model were included by LASSO. This may be explained by how LASSO handles multicollinearity and keeps the variable that has the strongest association among correlated variables. Perhaps patients who had received remdesivir or had symptoms  $> 10$  days at discharge reflected the same subgroup of patients that had more favorable clinical parameters peri-discharge. Even with a more parsimonious model, however, our primary analysis had a c-statistic of 0.76 compared to 0.80 with the all-variable model.

Unexpectedly, treatment with corticosteroids was not included by LASSO nor identified to be significantly associated with lower odds of 14-day all-cause readmission or mortality despite known mortality benefits in patients with COVID-19.<sup>31</sup> There are at least three potential explanations. First, corticosteroids became standard of care during our study period and close to 70% of our population had received corticosteroids, which may have limited our ability to detect meaningful differences. Second, our study occurred during the

early period of the pandemic where corticosteroid use had not been standardized, which may have confounded our findings. Alternatively, survivorship bias due to inclusion of only patients discharged alive may have resulted in selection of sicker patients that benefited from corticosteroids with subsequent complications that may have masked any potential benefits in disease burden reduction.

Our study has potential limitations. Our study period was relatively early in the pandemic which may limit the generalizability of our findings especially given the rapidly changing landscape of COVID-19 disease management, including vaccination which was not available until after our study period. Despite multivariable analysis, there remains the possibility of residual confounding, particularly with therapies received. There may also be survivorship bias as we only included patients discharged alive, though we believe this to less likely affect the findings regarding remdesivir, given remdesivir is not known to exhibit a significant mortality benefit.<sup>11</sup> We lacked granular details on therapies, particularly with regard to dosage and duration, and with regard to clinical parameters, due to categorization of the variables, though we believe this enhances the ability for these results to be interpreted by clinicians. Symptom duration can be highly subjective, though misclassification is likely reduced by dichotomous categorization of the variable. Data values for oxygen requirements and saturation were only limited to the last reading and may not accurately reflect the true clinical status of the patients. We also relied on multiple imputation for missing data, though a complete case sensitivity analysis yielded similar results. Finally, readmissions remain a complex healthcare problem and there may be unaccounted for factors despite the multitude of variables included.

At the same time, our study also has considerable strengths. Our focus on lesser studied variables adds novel findings to the limited literature regarding care transition for COVID-19 patients and benefited from a larger cohort.<sup>8</sup> We were also able to confirm our findings in multiple models and further identified a significant interaction between remdesivir and symptom duration which can further enhance the utility of these variables in clinical decision making. More importantly, our study design allowed us to explore multiple different variables of interest simultaneously. This approach precluded us from examining specific variables more closely, but it is hypothesis generating. Future studies are necessary to explore more granular aspects of the variables identified and whether they can serve as clinical indicators for safe hospital discharge.

In a real-world clinical setting, we observed treatment with remdesivir to be a protective factor and duration of symptoms  $\leq 10$  days to be a risk factor for 14-day all-cause readmission or mortality among patients discharged alive following hospitalization for COVID-19. Our findings support the consideration of whether a patient has been treated with remdesivir and symptom duration during times of uncertainty with discharge decisions. Oxygen requirements and afebrile duration at discharge may provide additional clinical targets.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11606-022-07610-5>.

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**Declarations:**

**Conflict of Interest:** The authors declare that they do not have a conflict of interest.

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