Readmission Risk after COVID-19 Hospitalization: A Moderation Analysis by Vital Signs

Arkadiy Finn, MD, Joshua R. Tanzer, PhD, Atin Jindal, MD, Vijairam Selvaraj, MD, Bradley Collins, MD, and Kwame Dapaah-Afriyie, MD

Objective: Readmission to the hospital after hospitalization with coronavirus disease 2019 (COVID-19) is associated with significant morbidity and mortality. Hospital clinicians may identify the presence of a patient's comorbid conditions, overall severity of illness, and clinical status at discharge as risk factors for readmission. Objective data are lacking to support reliance on these factors for discharge decision making. The objective of our study was to examine risk factors for readmission to the hospital after COVID-19 hospitalization and the impact of vital sign abnormalities, within 24 hours of discharge, on readmission rates.

Methods: In total, 2557 COVID-19-related hospital admissions within the Lifespan Health System, a large multicenter health system (Rhode Island), of 2230 unique patients aged 18 years and older, occurring from April 1, 2020 to December 31, 2020 were analyzed. Risk factors associated with readmission within 30 days were identified and analyzed using Cox regression. A moderation analysis by vital signs at discharge on the risk of readmission was performed.

Results: Clinical factors associated with readmissions included existing cardiovascular conditions (risk ratio 2.32, 95% confidence interval [CI] 1.10–4.90) and pulmonary disease (risk ratio 3.25, 95% CI 1.62–6.52). The absence of abnormal vital signs within 24 hours of discharge was associated with decreased 30-day readmission rates (risk ratio 0.70, 95% CI 0.52–0.94). Elevated C-reactive protein and D-dimer values and in-hospital complications including stroke, myocardial infarction, acute renal failure, and gastrointestinal bleeding were not associated with an increased risk of readmission. In moderation analysis, the presence of normal vital signs within 24 hours of discharge was associated with decreased readmission risk in patients who had primary risk factors for readmission including pulmonary disease (risk ratio 0.80, 95% CI 0.65–0.99), psychiatric disorders, and substance use (risk ratio 0.70, 95% CI 0.52–0.94).

Conclusions: Comorbid conditions, including pulmonary and cardiovascular disease, are associated with readmission risk after COVID-19 hospitalization. The normalization of vital signs within 24 hours of discharge during COVID-19 hospitalization may be an indicator of readiness for discharge and may mitigate some readmission risk conferred by comorbid conditions.

Key Words: 30-day readmission, COVID-19, discharge, mortality, vital signs

In the United States, 2.2 million hospital admissions for coronavirus disease 2019 (COVID-19), the syndrome caused by severe acute respiratory syndrome-coronavirus-2, occurred from August 1, 2020 to June 26, 2021.[1] Postdischarge outcomes for COVID-19 hospitalization are of particular interest to clinicians as 4% to 20% of patients are readmitted to the hospital within 60 days of discharge, with mortality rates upon readmission ranging between 12% and 30%.[2–8] The clinician is faced with a complex decision-making challenge when evaluating a patient's readiness for discharge during COVID-19 hospitalization. Prolonged hospital length of stay may be associated with morbidity through iatrogenic complications, whereas discharge followed by readmission within 30 days is associated with significant mortality and morbidity.[9] Within regions experiencing surge levels of COVID-19 hospitalizations, clinicians may encounter limited hospital bed availability and face additional pressure to

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Key Points

- Normalization of vital signs at discharge was associated with a reduced risk of 30-day readmission after coronavirus disease 2019 (COVID-19) hospitalization.
- COVID-19 patients with high-risk primary factors, including behavioral health conditions, immunocompromised status, and pulmonary disease may be at greatest need for stable vital signs before discharge.
- The presence of more than two vital sign abnormalities within 24 hours of discharge should be interpreted with caution by the discharging clinician and may prompt further observation.

make the "correct" decision regarding which COVID-19 patients are safe to discharge from the hospital.

The clinician may consider the patient's comorbid conditions, overall severity of illness, and clinical status in discharge decision making.[10] We chose to evaluate certain high-risk comorbid conditions, COVID-19 disease severity as represented by elevated serum inflammatory markers (C-reactive protein [CRP], D-dimer) and in-hospital complications, and vital signs within 24 hours of discharge and their associations with 30-day hospital readmission. Frontline clinicians are likely to have access to this information and may benefit from understanding its impact upon readmission risk. Our hypothesis was that the presence of abnormal vital signs within 24 hours of discharge may have a strong effect on readmission risk in COVID-19. Our aim was to provide insights into how to identify and mitigate readmission risk in COVID-19 at the time of discharge from the hospital.

Methods

Sample

From April 1, 2020 to December 31, 2020, there were 2557 COVID-19–related hospital admissions of 2230 unique patients aged 18 years and older within the Lifespan Health System, a large multicenter health system in Rhode Island. All of the patients identified tested positive for the presence of severe acute respiratory syndrome-coronavirus-2 via nasopharyngeal swab or serum serology testing. The combined Lifespan institutional review board approved the study protocol. Details regarding the clinical course, rehospitalizations, and/or deaths were abstracted from the electronic health records.

We analyzed a large sample of inpatients with COVID-19 to identify risk factors associated with readmission within 30 days and performed a moderation analysis by vital signs at discharge. We identified broad categories of clinical variables, including demographics, comorbid conditions, functional status, laboratory testing, hospital complications occurring during admission, pharmacologic treatments, and vital signs within 24 hours of discharge (see Table 1 for a list of all of the conditions and Supplemental Digital Content Appendix 1A [http://links.lww.com/SMJ/A306] for *International Classification of Diseases, Tenth Revision* codes used for the identification of comorbid conditions). Clinical variables were selected on the basis of relevance to discharge decision making, such as comorbid conditions that are known to be associated with readmissions.[11,12] Other variables were selected for clinical relevance because these would be available to the treating clinician, including elevated serum inflammatory markers and certain in-hospital complications that include cardiac events, neurological events, acute renal failure, gastrointestinal bleeding, and venous thromboembolism. In-hospital complications were identified from chart review (Supplemental Digital Content

Table 1. Sample characteristics

Variable	N	%
Demographics		
Older than 65 y	1248	48.81
Hispanic primary racial identity	815	31.87
Speaks English as primary language	1733	67.77
On Medicare/Medicaid	997	38.99
Discharge to SNF/ALF	330	12.91
Uses tobacco	912	35.67
Uses substances	253	9.89
Uses alcohol	112	4.38
Died	349	13.65
Comorbidities		
Cardiac disease	1129	44.15
Diabetes mellitus	1038	40.59
Obesity	150	5.87
Endocrine disorder	73	2.85
Pulmonary disease	979	38.29
Neurological disease	622	24.33
Chronic kidney disease	549	21.47
Malignancy	448	17.52
Hematologic disorder	671	26.24
Psychiatric disorder	1054	41.22
Gastrointestinal disease	90	3.52
Immunocompromised status	380	14.86
Functional status		
New difficulties with ADLs	426	16.66
Extensive or total dependence on at least 1 ADL	591	23.11
Live at private residence	1366	53.42
Self-reported severe disability	346	13.53
Recent unexpected weight loss	73	2.85
Recent hospitalization	326	12.75
Laboratory tests[a]		
Low albumin	1196	51.62
Low ALT	1799	77.44
Low AST	1879	80.89
Low CRP	1105	56.09
Low D-dimer	1677	82.37
Low troponin	1948	93.43
Low white blood cell count	1601	64.35
Low lymphocytes	1361	54.92
Low eGFR	822	33.46
Medication use		
Remdesivir	758	29.64
Antibiotics	1379	53.93
Diuretics	814	31.83
Steroids	1002	39.19
Anticoagulants	809	31.64

ADL, activity of daily living; ALF, assisted living facility; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; SNF, skilled nursing facility.
[a]Test values were continuous values dichotomized relative to the sample mean.

Appendix 1B, http://links.lww.com/SMJ/A306). Readmissions were ascertained within the Lifespan Health System, the largest hospital system provider in Rhode Island, accounting for most of the state's COVID-19 admissions during the study period.

Analysis Plan

The goal of the analysis was to understand which patients may have been at greatest risk for readmission who could benefit from further vital sign stabilization before discharge. This was accomplished using Cox regression.[13] In this method, the proportional hazards of an adverse event are modeled as a dynamic function of time and specified covariates. The continuous number of days before binary readmission were modeled within the sample. Patient risk groups emphasized behavioral health (substance use, psychiatric disorders), comorbidities (cardiac disease, pulmonary disease, immunocompromised status), and laboratory tests (CRP, D-dimer).

Interaction terms were included between variables within conceptual groups to allow for their possible co-occurrence. In addition, an interaction was included between immunocompromised status, CRP, and D-dimer, because these were the patients who were thought to be at greatest risk for severe COVID-19 disease. Lastly, in-hospital events were included to identify whether experience during the hospital stay was associated with increased risk, specifically cardiac events, renal events, neurological events, venous thromboembolic events, and gastrointestinal bleeding events. Length of hospital stay was included as an event of interest, out of concern that longer hospital stays may be associated with worse prognosis because of the severity of the case.[14] All of the variables but length of stay were measured as binary indicators, in which 1 represents presence of condition and 0 represents absence of condition. In the case of CRP and D-dimer, a 1 represented that the patient was above the sample average and a 0 represented that the patient was below the

Table 2. Readmission risk and moderation effects by vital signs at discharge

Variable	Primary effects		Moderation effects	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Vital signs				
Vital signs	—	—	0.70	0.52–0.94
Vital signs (quadratic)	—	—	1.07	1.02–1.12
Behavioral health				
Substance use	0.38	0.16–0.92	1.64	1.29–2.09
Psychiatric disorder	1.08	0.82–1.43	1.03	0.93–1.14
Psychiatric disorder and substance use	2.21	0.70–6.96	0.70	0.52–0.94
Comorbidities				
Cardiac disease	2.32	1.10–4.90	0.94	0.75–1.18
Pulmonary disease	3.25	1.62–6.52	0.80	0.65–0.99
Immunocompromised status	1.71	0.46–6.42	0.91	0.66–1.25
Cardiac and pulmonary disease	0.74	0.31–1.78	1.16	0.86–1.56
Cardiac disease and immunocompromised status	0.98	0.27–3.62	1.18	0.77–1.80
Pulmonary disease and immunocompromised status	0.58	0.14–2.33	1.72	1.18–2.51
Cardiac and pulmonary disease, immunocompromised status	0.66	0.19–2.34	0.50	0.29–0.86
Laboratory tests				
High CRP	0.85	0.55–1.32	1.05	0.91–1.21
High D-dimer	1.42	0.83–2.44	1.14	0.96–1.36
High CRP and D-dimer	0.89	0.46–1.71	1.05	0.81–1.36
Immunocompromised status and high CRP	1.09	0.46–2.60	0.90	0.69–1.17
Immunocompromised status and high D-dimer	1.48	0.51–4.28	0.73	0.45–1.20
Immunocompromised status and high CRP and D-dimer	1.44	0.26–8.10	1.11	0.62–1.98
Hospital events				
Cardiac event	0.81	0.37–1.76	1.00	0.72–1.39
Renal event	0.39	0.18–0.82	1.19	0.97–1.46
Neurological event	0.99	0.52–1.90	1.01	0.83–1.23
Gastrointestinal event	1.12	0.38–3.26	1.07	0.82–1.39
Length of stay	0.99	0.98–1.00	1.00	0.99–1.01

Primary effects represent the average risk for each specified trait. Moderation effects represent the unique linear association between vital signs and each specified trait, beyond the reported overall average. CI, confidence interval; CRP, C-reactive protein.

sample average. Lastly, random intercepts were estimated by individual because some patients had multiple hospitalizations.

To identify the patient groups that may be more susceptible to intervention, moderation analysis was used. Patients discharged with fewer abnormal vital signs in the 24 hours prior to before discharge were expected to have a reduced risk of readmission. Possible moderation by patient vital signs at discharge was included for all of the variables, as the linear interaction between vital signs and each variable in the analysis.

Abnormal vital signs were defined by five components: hypotension, fever, hypoxia, tachycardia, and respiratory rate. The threshold for abnormality was a single abnormal reading within 24 hours of discharge. Fever was defined by body temperature > 100.5 °F. Hypotension was defined by systolic blood pressure < 90 mm Hg. Tachycardia was defined as a heart rate > 110 beats per minute. Tachypnea was defined as a respiratory rate > 30 breaths per minute. Hypoxia was defined as ≤90% arterial oxygen saturation by digital probe pulse oximetry.

Scores were rated on a scale from 0 (representing not ready for discharge, all vital signs are abnormal) to 5 (representing readiness for discharge, no vital signs are abnormal). To ensure that this approach was appropriate for the data, a brief measurement analysis was performed. Reliability was estimated using principal-components analysis.[15] A one-factor solution was estimated, because it was believed that the vital signs were measuring the single aspect of patient readiness for discharge. This was supported by a large single eigenvalue greater than all of the others, and all loadings positive and significant. This indicates that all of the vitals were reasonably correlated together. Lastly, coefficient omega reliability was estimated to be above the research standard of 0.70 (omega 0.83), providing support that the vital signs scale was reliable.

Next, a check of measure validity was performed. Patients with more normal vital signs tended toward significantly shorter lengths of stay (rho −0.45, $P < 0.0001$) and significantly reduced probability of readmission (rho −0.12, $P < 0.0001$). Visual examination of the plots of these pairwise relationships revealed a linear relationship. There was some evidence of a curvilinear trend such that patients with the worst vitals were at greatest risk, and patients with the best vitals were not at the lowest risk. For this reason, a quadratic component was added to the final analysis model, to account for possible heterogeneity of patient risks above the primarily linear association. Although a quadratic trend may seem counterintuitive, if no such association exists, then the parameter will be close to zero and nonsignificant. These results provide support that the patient vital signs scale was reliable and a valid measure for estimating patient readiness for discharge.

Results

Sample characteristics are reported in Table 1. The sample had a wide distribution of ages, with approximately half of patients older than 65 years (48.81%), and approximately one-third of the sample identifying as being of Hispanic primary racial identity (31.87%). Approximately two-fifths of patients indicated Medicare/Medicaid as their primary insurer (38.99%). In total, 21.20% of patients were readmitted and 13.65% of patients did not survive index hospitalization.

Table 2 presents the primary effects identifying patient risk groups and the moderation analysis results. Most of the primary effects were not statistically significant or if they were significant, they also indicated possible moderation. The one primary effect that did not indicate evidence of moderation was the presence of renal events. Patients with renal events during their hospital stay were at reduced readmission risk on average (hazard ratio 0.39, 95% confidence interval [CI] 0.18–0.82).

The hazard ratios of 30-day readmission across vital sign condition are plotted in the Figure. As anticipated, patients with fewer vital sign abnormalities before discharge tended toward a reduced risk of readmission (risk ratio 0.70, 95% CI 0.52–0.94). The quadratic term also was significant, indicating that the patients with the greatest number of abnormal vital signs were
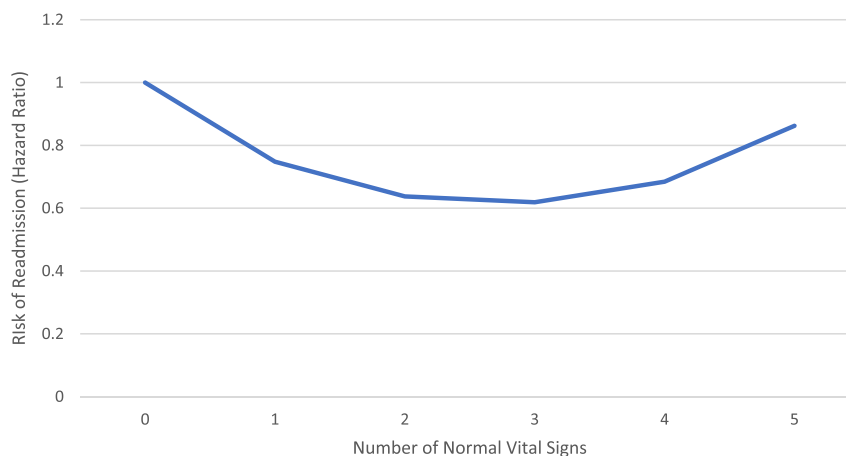

Fig. Changes in risk ratio across vital signs. This relationship may be interpreted as a general trend because the moderated relationships listed in Table 2 had more statistical significance.

at highest risk, and that the patients with the best vital signs were not at the lowest risk (risk ratio 1.07, 95% CI 1.02–1.12).

Examinations of patient traits found that patients with psychiatric disorders and reported substance use who had a greater number of normal vital signs at discharge were at significantly reduced risk of readmission (risk ratio − 0.70, 95% CI 0.52–0.94). Certain comorbidities also demonstrated statistical significance, with patients identified as immunocompromised status in addition to cardiac and pulmonary disease being at heightened risk if vital signs were not normalized before discharge (risk ratio 0.50, 95% CI 0.29–0.86). More specifically, patients with pulmonary disease were at heightened risk, in general (risk ratio 3.25, 95% CI 1.62–6.52). This was mitigated by ensuring a stable vital signs condition before discharge (risk ratio = 0.80, 95% CI 0.65–0.99). None of the laboratory tests or hospital events indicated moderation by vital sign status.

Discussion

Primary risk factors associated with readmission after COVID-19 hospitalization included cardiovascular and pulmonary conditions. The normalization of vital signs within 24 hours of discharge was associated with decreased 30-day readmission rates. We found no evidence that either elevated peak CRP and D-dimer values or in-hospital complications, including stroke, myocardial infarction, acute renal failure, and gastrointestinal bleeding, were associated with an increased risk of readmission within 30 days. In moderation analysis, the presence of normal vital signs was associated with decreased readmission risk in patients who had primary risk factors for readmission, including pulmonary disease, psychiatric disorders, and substance use, as well as pulmonary disease and immunocompromised status. Our results suggest that the normalization of vital signs within 24 hours of discharge after COVID-19 hospitalization may be an indicator of readiness for discharge and may mitigate some of the readmission risk conferred by primary factors.

Readmission to the hospital after COVID-19 hospitalization carries significant morbidity and mortality risks.[2–8] Table 3 shows reported readmission rates, primary diagnosis, and outcomes upon readmission. Readmission may occur related to the exacerbation of underlying comorbid conditions and/or progression of organ failure related to COVID-19. Multiple reports point to associations between various comorbid conditions, including cardiovascular disease, diabetes mellitus, chronic kidney disease, substance use disorders, and hospital readmission in COVID-19.[16–23] Comorbid conditions also have strong associations with readmission in other conditions requiring hospitalization, including influenza, congestive heart failure, and chronic obstructive pulmonary disease.[14,24,25] Our analysis is broadly consistent with findings from other reports that underlying pulmonary and cardiac disorders are among the primary risk factors for readmission after COVID-19 hospitalization.

COVID-19 disease severity, as indicated by elevated serum markers of inflammation such as CRP and D-dimer, was evaluated as a prognostic marker for readmission. Serum inflammatory markers are widely accepted as indicators of severity of

Table 3. Studies with >500 patients reporting rates of readmissions in COVID-19 hospitalization

	No. index admissions with COVID-19	30-day readmission rate, %	Readmission primary diagnosis (%)	Mortality upon readmission, %
Banerjee et al[2]	621	8.5	Not reported	1.3
Donnelly et al[3]	2179	19.9 (60-d readmission)	COVID-19 (30.2) Sepsis (8.5) Pneumonia (3.1)	Not reported
Jeon et al[4]	7590	4.5	Not reported	Not reported
Lavery et al[5]	106,543	7.5	COVID-19 (45) Diseases of the circulatory system (11) Diseases of digestive systems (7)	Not reported
Parra et al[6]	1368	4.4	Pneumonia (55.7) Pulmonary thromboembolism (13.1) Heart failure (9.8)	14.7
Somani et al[7]	2864	2.0	Respiratory distress (50) Other (22) Chest pain (6)	5.4
Yeo et al[8]	1062	4.5	Hypoxic respiratory failure (68.8) Thromboembolism (12.5) Sepsis (6.3)	22.9

COVID-19, coronavirus disease 2019.

disease in COVID-19, correlate with disease responsiveness to treatment, and are available in clinical practice.[26,27] We did not observe a significant association between elevated peak CRP and D-dimer levels and readmission rates. Elevated peak serum inflammatory markers may be stronger indicators of in-hospital mortality over readmission risk. Hospital events, including cardiac, neurological, renal, venous thromboembolic, and gastrointestinal bleeding, also did not demonstrate evidence of an association with an increased risk of readmission. Complications occurring in the hospital also may be expected to confer mortality risk in COVID-19. Patients who survive hospitalization may not be so severely affected by these events that they need to return to the hospital within 30 days for further treatment.

Vital signs play an important role in real-time decision making regarding discharge from the hospital. We observed a strong association between the number of abnormal vital signs (range 0–5) within 24 hours of discharge and an increased risk of readmission after COVID-19 hospitalization. Vital sign instability in the 24 hours before discharge was reported in association with increased 7-day readmission rate in patients hospitalized for a broad range of disorders.[28] Presence of any (≥1) vital sign instability was associated with a higher odds of either death or 30-day readmission for patients discharged from a general inpatient medical service.[29] Assessing the stability of a patient's vital signs in the 24 hours before discharge provides an objective and intuitive approach to determining discharge readiness in COVID-19. Our findings suggest that the presence of more than two vital sign abnormalities within 24 hours should be interpreted with caution by the discharging clinician and may prompt further observation.

Moderation analysis evaluates the interaction between a relevant external variable and primary effects, significance indicating that patient risks depended on the levels of the moderator variable.[30] A moderator variable can be conceptualized as a possible target of intervention. The hypothesized target intervention in this analysis was vital signs within 24 hours of discharge. In patients with primary risk factors for readmission, including substance use and pulmonary disease, we show that the normalization of vital signs within 24 hours of discharge is associated with a reduced risk of subsequent readmission. This is an application of an analytic technique to clinical decision making and should not be interpreted to infer causality. Our analysis provides the following approach to discharge decision making for hospitalized COVID-19 patients: consideration of readmission risk factors with a focus upon comorbid conditions, followed by an assessment of recorded vital signs, with the likelihood of readmission decreasing as the number of normal vital signs increases. Clinicians should continue to heed other considerations in discharge decision making, including unresolved symptoms, physical examination findings, functional status, and other patient-specific concerns.

The primary limitation of this study is its observational design. To address this, future research may endeavor to design an intervention targeting discharge preparedness. For example, if a checklist were developed specifying criteria that patients needed to meet before discharge, then readmission among patients who randomly received the checklist could be compared with readmission among patients receiving usual care. This limitation is further complicated by the nature of the COVID-19 pandemic as hospitals were faced with increasing patient volume, which may have factored into real-world discharge decision making. The sample had a high rate of 30-day readmission events (approximately 21%) and may not be generalizable in comparison with other published data. In addition, some patients may have been readmitted outside of our hospital system, which may have led to an underestimation of the overall number of readmissions. Lastly, the quadratic association does complicate the direct interpretation of results as patients released with completely stable vitals were not the least likely to readmit. This may be because patients retained until all vitals have stabilized had severe health conditions. These patients would then be at a higher risk of readmission, not because they were unprepared for discharge, but because they were at high risk to begin with. An experimental evaluation of this association would be informative.

Conclusions

The normalization of vital signs at discharge was associated with a reduced risk of 30-day readmission after COVID-19 hospitalization. A moderation analysis revealed that patients with high-risk primary factors including behavioral health conditions, immunocompromised status, and pulmonary disease have the greatest need for a stable clinical condition, as represented by vital signs, before discharge. The clinician, who must balance the potential risks and benefits of discharge timing, may incorporate the normalization of vital signs within 24 hours of discharge as a criterion in decision making during COVID-19 hospitalization.

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