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Readmissions, Postdischarge Mortality, and Sustained Recovery Among Patients Admitted to Hospital With Coronavirus Disease 2019 (COVID-19)

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Background. Many interventional in-patient coronavirus disease 2019 (COVID-19) trials assess primary outcomes through day 28 post-randomization. Since a proportion of patients experience protracted disease or relapse, such follow-up period may not fully capture the course of the disease, even when randomization occurs a few days after hospitalization.

Methods. Among adults hospitalized with COVID-19 in eastern Denmark from 18 March 2020–12 January 2021 we assessed all-cause mortality, recovery, and sustained recovery 90 days after admission, and readmission and all-cause mortality 90 days after discharge. Recovery was defined as hospital discharge and sustained recovery as recovery and alive without readmissions for 14 consecutive days.

Results. Among 3386 patients included in the study, 2796 (82.6%) reached recovery and 2600 (77.0%) achieved sustained recovery. Of those discharged from hospital, 556 (19.9%) were readmitted and 289 (10.3%) died. Overall, the median time to recovery was 6 days (interquartile range [IQR]: 3–10), and 19 days (IQR: 11–33) among patients in intensive care in the first 2 days of admission.

Conclusions. Postdischarge readmission and mortality rates were substantial. Therefore, sustained recovery should be favored to recovery outcomes in clinical COVID-19 trials. A 28-day follow-up period may be too short for the critically ill.

Keywords. COVID-19; sustained recovery; readmission; postdischarge mortality; SARS-CoV-2.

Previous studies have indicated that some patients with coronavirus disease 2019 (COVID-19) have protracted disease and that rates of postdischarge mortality and readmissions can be substantial [1, 2]. This could potentially have affected the validity of results of clinical trials, since many interventional clinical trials of COVID-19 treatments evaluated outcomes at day 28 after randomization [3–9]. Reported estimates on length of hospital stay for patients with COVID-19 with critical illness vary, but exceeds 28 days since admission for a notable proportion of the critically ill patients in some studies [10, 11]. For such patients, a primary outcome assessed during a 28-day follow-up period may not capture the full course of the disease, and also may cover little or none of the postdischarge time period after initial recovery. Further, if rates of readmissions and postdischarge deaths are substantial, a significant number of patients classified as recovered may not truly have recovered from COVID-19. The Accelerating COVID-19 Therapeutic Interventions and Vaccines 3 (ACTIV-3): Therapeutics for Inpatients With COVID-19 (TICO) trial, a large multisite trial of multiple treatments for hospitalized patients with COVID-19, introduced the outcome of "sustained recovery." Sustained recovery was defined as discharge from hospital and remaining alive and discharged for 14 days, thereby accounting for postdischarge readmissions and deaths in treatment effect estimates [12, 13]. This definition was developed in July 2020 and was based on preliminary findings from cohort studies including the one described here.

To evaluate sustained recovery as an outcome and to assess the optimal time point to estimate rates of sustained recovery, we examined longer-term all-cause mortality, postdischarge mortality, readmissions, recovery, and sustained recovery among patients hospitalized with COVID-19. In secondary analyses, we compared these outcomes (1) before and after dexamethasone and remdesivir were introduced as standard of care and (2) between subgroups defined by disease severity during index admission.

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METHODS

Study Setting

This study was a multicenter cohort study in eastern Denmark, a region with 2.7 million inhabitants. All patients with COVID-19 in need of in-patient care treated at public hospitals were eligible for this study. A total of 10 hospitals contributed with data to this study. All hospitals used an identical software, Sundhedsplatformen, for electronic health records (EHRs), by Epic [14]. During surges of COVID-19–related hospital admissions it was necessary to postpone elective surgery and reallocate hospital resources, but the capacity for hospital admissions and intensive care was not saturated at any point in time. In June 2020, remdesivir and dexamethasone were introduced as standard of care in treatment of patients with COVID-19 in Denmark. Community transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was low in June 2020 and this time point separated the first and second wave of COVID-19–related hospital admissions.

Data Sources

Data were obtained from EHRs and merged with data on vital status from the Danish civil registration system, using the unique civil registration number that is assigned to all Danish citizens, ensuring near-complete ascertainment of mortality. Data freeze was 26 May 2021.

Study Population

We included adult patients, aged 18 years and older, admitted to a hospital with an International Classification of Diseases, 10th Revision (ICD-10), diagnosis code of COVID-19 between 18 March 2020 and 12 January 2021, and fulfilling the following criteria: a positive SARS-CoV-2 polymerase chain reaction (PCR) test between 30 days before and 7 days after the date of admission, duration of hospital admission more than 48 hours, and at least 1 measurement of vital signs during this admission. The first admission fulfilling these criteria was defined as the "index admission." The inclusion criteria of both a measurement of vital signs and at least a 48-hour in-patient stay were introduced, since outpatients who visited hospitals for COVID-19 tests were included on inpatient EHR lists in some hospitals during March 2020. Further, the 48-hour criterion was introduced to include only patients who had moderate/severe COVID-19 and to be comparable to patients included in clinical trials of patients hospitalized with COVID-19, and who are often randomized a few days after admission.

Definitions

Baseline was defined as time of index admission. A subsequent admission with a duration of more than 48 hours and within 90 days after discharge of the index admission was categorized as a readmission. If a hospital admission occurred less than 48 hours after discharge from a previous admission, the 2 admissions were regarded as 1 admission. Patients with index admissions of more than 90 days were excluded from analysis of postdischarge outcomes. Discharge was defined as the date of discharge from the hospital as we did not have information on whether patients were discharged to their home, elderly homes, rehabilitation, etc.

Disease severity was assessed by the maximum levels of respiratory support given until different time points of the index admission and categorized for each patient on an ordinal scale grouped as 0–5 L O_2/minute, more than 5–15 L O_2/minute, more than 15 L O_2/minute without intensive care unit (ICU) admission, or ICU admission.

Comorbidities at baseline were determined using ICD-10 codes from hospital records prior to the index admission and categorized in meta-categories from the Charlson comorbidity index and the Elixhauser index [15, 16]. The complete ICD-10 categorization used is available in Supplementary Table 1.

Outcomes

The outcomes were "death within 90 days from index admission," "death within 90 days from discharge from index admission," "readmission within 90 days from discharge from index admission," and a combined endpoint of "readmission or death (whichever came first) within 90 days from discharge from index admission," "recovery within 90 days from index admission," and "sustained recovery within 90 days from index admission." Recovery was defined as discharge from index admission. Sustained recovery was defined as discharge from the index admission and being alive without readmissions for 14 consecutive days. If a patient was readmitted before reaching sustained recovery, the 14-consecutive-day event-free period could be achieved after discharge from a readmission.

Statistical Analyses

All patients were included from 48 hours after the index admission to the outcome of interest or "90 days after index admission" or "90 days after discharge from index admission," as specified in the outcomes or freeze date of 26 May 2021. Patient characteristics were presented overall, stratified by wave, and stratified by the maximum disease severity in the first 14 days of index admission. The Kaplan-Meier method was used to estimate the risk of "death within 90 days after index admission," "death within 90 days after discharge from index admission," and "readmission or death within 90 days after discharge from index admission." "Recovery with 90 days after index admission," "sustained recovery with 90 days after index admission," and "readmission within 90 days after discharge from index admission" were illustrated by cumulative incidence curves. In analysis stratified for disease severity, we stratified by the maximum level of respiratory support in the first 2 and 14 days of index admission. Recovery could first occur 2 days after the index admission due to the inclusion criteria. Sustained recovery could first occur from day 16 since the index

admission, due to the outcome definition and inclusion criteria. Multivariable Cox regression analysis assessed the factors associated with "death" and "readmission or death" by comparing cause-specific hazards. Multivariable Fine-Gray models compared the sub-distribution hazard for "recovery," "sustained recovery," and "readmission." Variables of interest included wave, age, sex, and individual comorbidities of cardiovascular disease, hypertension, diabetes mellitus, chronic pulmonary disease, renal disease, malignancy, neurological disease, and moderate to severe liver disease defined from the comorbidities meta-categories. The statistical software R and the packages *survival*, *mstate, cmprisk* and *tidyverse* were used for data analyses (R Foundation for Statistical Computing).

RESULTS

Study Population

We included 3386 adult patients admitted to a hospital with COVID-19 in the study period: 1137 and 2249 in the first and second waves, respectively (see Supplementary Figure 1). The median age was 74 years (interquartile range [IQR]: 61–82 years) and 54.7% were male. The duration of the index admission was a median of 6.8 days (IQR: 4.1–11.7 days) and 590 died during the index admission (Table 1). The baseline characteristics were similar between patients admitted during the first and the second wave. Baseline characteristics of the total cohort and survivors of the index admission are summarized in Table 1. Characteristics stratified by disease severity during the index admission are summarized in Supplementary Table 2 and for survivors of the index admission in Supplementary Table 3. Data on treatment with remdesivir and dexamethasone in the first and second wave are displayed in Supplementary Table 4.

Overall Outcomes

In the total cohort, 2796 (82.6%) were discharged within 90 days after admission (Table 2), and thereby reached the outcome of "recovery"; 861 patients (25.4%; 95% confidence interval [CI]: 24.0–26.9%] died within 90 days from the index admission (Figure 1*A*).

Readmissions and Postdischarge Mortality

Of the 2796 who recovered, 19.9% had been readmitted 90 days after initial recovery (Figure 1*C*), with 10.9% (95% CI: 9.8–12.1%) readmitted after 14 days. In total, 10.3% (95% CI: 9.2–

Table 1. Patient Characteristics

Variable	All Patients			Recovery Within 90 Days From Index Admission		
	Total Cohort (N = 3386)	First Wave[a] (n = 1137)	Second Wave[b] (n = 2249)	Total Cohort (N = 2796)	First Wave[a] (n = 872)	Second Wave[b] (n = 1924)
Patient age, n (%)						
18 to 49 y	371 (11.0)	126 (11.1)	245 (10.9)	367 (13.1)	124 (14.2)	243 (12.6)
50 to 69 y	978 (28.9)	340 (29.9)	638 (28.4)	874 (31.3)	290 (33.3)	584 (30.4)
70 to 79 y	928 (27.4)	325 (28.6)	603 (26.8)	757 (27.1)	241 (27.6)	516 (26.8)
80 to 100 y	1109 (32.8)	346 (30.4)	763 (33.9)	798 (28.5)	217 (24.9)	581 (30.2)
Male, n (%)	1852 (54.7)	622 (54.7)	1230 (54.7)	1498 (53.6)	455 (52.2)	1043 (54.2)
Comorbidities at baseline, n (%)						
Cardiovascular disease	1237 (36.5)	378 (33.2)	859 (38.2)	945 (33.8)	269 (30.8)	676 (35.1)
Hypertension	815 (24.1)	256 (22.5)	559 (24.9)	639 (22.9)	188 (21.6)	451 (23.4)
Diabetes mellitus	567 (16.7)	186 (16.4)	381 (16.9)	438 (15.7)	133 (15.3)	305 (15.9)
Chronic pulmonary disease	481 (14.2)	153 (13.5)	328 (14.6)	382 (13.7)	114 (13.1)	268 (13.9)
Renal disease	231 (6.8)	72 (6.3)	159 (7.1)	157 (5.6)	47 (5.4)	110 (5.7)
Malignancy	443 (13.1)	136 (12.0)	307 (13.7)	343 (12.3)	95 (10.9)	248 (12.9)
Neurological disease	412 (12.2)	143 (12.6)	269 (12.0)	301 (10.8)	90 (10.3)	211 (11.0)
Moderate/severe liver disease	18 (0.5)	6 (0.5)	12 (0.5)	15 (0.5)	4 (0.5)	11 (0.6)
Median (IQR) time from index admission to PCR test, d	0.3 (–2.9 to 0.7)	0.4 (–1.5 to 0.6)	0.3 (–3.4 to 0.8)	0.3 (–3.2 to 0.7)	0.4 (–2.5 to 0.6)	0.3 (–3.5 to 0.8)
Duration of index admission, median (IQR), d	6.8 (4.1–11.7)	7.3 (4.2–13.2)	6.4 (4.0–10.7)	6.1 (4.0–10.6)	7.0 (4.1–13.0)	6.0 (4.0–9.8)
Died during index admission, n (%)	590 (17.4)	265 (23.3)	325 (14.4)	0 (0.0)	0 (0.0)	0 (0.0)
Maximum level of respiratory support in first 14 d of index admission, n (%)						
<5 L O_2/minute	2111 (62.3)	642 (56.5)	1469 (65.3)	2018 (72.2)	610 (70.0)	1408 (73.2)
5–15 L O_2/minute	509 (15.0)	181 (15.9)	328 (14.6)	368 (13.2)	120 (13.8)	248 (12.9)
>15 L O_2/minute	348 (10.3)	140 (12.3)	208 (9.2)	150 (5.4)	49 (5.6)	101 (5.2)
ICU, n (%)	418 (12.3)	174 (15.3)	244 (10.8)	260 (9.3)	93 (10.7)	167 (8.7)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; PCR, polymerase chain reaction.

[a]Patients admitted to index admission 15 before June 2020.

[b]Patients admitted to index admission 15 after June 2020.

Table 2. Outcomes in Analyses in the Total Cohort, Stratified by Study Period and Level of Respiratory Support in the First 14 Days of Index Admission

				Respiratory Support			
	Total Cohort	First Wave[a]	Second Wave[b]	0–5 L/Minute	5–15 L/Minute	>15 L/Minute	ICU
Mortality							
n	3386	1137	2249	2111	509	348	418
Median (IQR) time from admission, d	11 (6–22)	10 (6–18)	13 (7–25)	…	…	…	…
Cumulative incidence, day 28, (95% CI)[c]	20.7 (22.1, 19.4)	24.8 (22.3, 27.3)	18.7 (17.1, 20.3)	…	…	…	…
Cumulative incidence, day 90, (95% CI)	25.4 (23.9, 26.9)	29.6 (26.8, 32.2)	23.3 (21.6, 25.1)	…	…	…	…
Hazard ratio, day 28, (95% CI)	…	…	0.65 (0.56, 0.75)	…	…	…	…
Hazard ratio, day 90, (95% CI)	…	Ref	0.67 (0.59, 0.77)	…	…	…	…
Postdischarge mortality							
n	2796	872	1924	2018	368	150	260
Median (IQR) time from discharge, d	13 (5–33)	14 (6–38)	13 (5–32)	14 (5–35)	10 (4–21)	18 (5–47)	16 (12–18)
Cumulative incidence, day 14, (95% CI)	5.4 (4.6, 6.2)	4.8 (3.4, 6.2)	5.7 (4.6, 6.7)	5.4 (4.4, 6.3)	9.0 (6.0, 11.8)	4.7 (1.2, 8.0)	1.2 (0.0, 2.4)
Cumulative incidence, day 90, (95% CI)	10.3 (9.2, 11.5)	9.1 (7.1, 10.9)	10.9 (9.5, 12.3)	10.6 (9.3, 11.9)	13.9 (10.3, 17.3)	10.7 (5.6, 15.5)	3.0 (1.0, 5.2)
Hazard ratio, day 14, (95% CI)	…	Ref	1.01 (0.70, 1.46)	Ref	0.58 (0.37, 0.92)	0.29 (0.13, 0.66)	0.25 (0.06, 1.04)
Hazard ratio, day 90, (95% CI)	…	Ref	1.08 (0.84, 1.40)	Ref	1.53 (1.12, 2.08)	1.13 (0.68, 1.88)	0.58 (0.28, 1.19)
Readmission[d]							
n	2796	872	1924	2018	368	150	260
Median (IQR) time from discharge, d	12 (4–39)	21 (5–48.75)	10 (4–36.75)	12 (5–38.25)	11 (4–42)	11 (4.5–32.5)	9 (3.75–32.75)
Cumulative incidence, day 14, (95% CI)[d]	10.9 (9.8–12.1)	7.6 (5.8–9.3)	12.5 (11.0–14.0)	11.2 (9.9–12.6)	10.3 (7.2–13.4)	12.0 (6.8–17.2)	8.8 (5.4–12.3)
Cumulative incidence, day 90, (95% CI)[d]	19.9 (18.4–21.4)	17.2 (14.7–19.7)	21.1 (19.3–22.9)	20.8 (19.0–22.6)	18.8 (14.8–22.7)	20.7 (14.2–27.1)	13.8 (9.7–18.0)
Risk ratio, day 14, (95% CI)[e]	…	Ref	1.58 (1.2, 2.07)	Ref	0.94 (0.67, 1.32)	1.05 (0.65, 1.71)	1.03 (0.66, 1.6)
Risk ratio, day 90, (95% CI)[e]	…	Ref	1.18 (0.98, 1.43)	Ref	0.90 (0.69, 1.17)	0.97 (0.68, 1.38)	0.87 (0.62, 1.24)
Readmission or postdischarge mortality							
n	2796	872	1924	2018	368	150	260
Median (IQR) time from discharge, d	10 (4–33)	14 (4–41)	9 (4–30)	10 (4–33)	7 (3 -32)	11 (4–30)	10 (4–28)
Cumulative incidence, day 14, (95% CI)	15.2 (13.9, 16.5)	11.6 (9.4, 13.7)	16.8 (15.2, 18.5)	15.6 (14.0, 17.2)	16.8 (12.9, 20.6)	16.0 (9.9, 21.7)	9.2 (5.6, 12.7)
Cumulative incidence, day 90, (95% CI)	25.8 (24.1, 27.4)	22.9 (20.1, 25.7)	27.1 (25.1, 29.0)	26.8 (24.9, 28.7)	27.2 (22.5, 31.6)	27.3 (19.8, 34.1)	15.0 (10.5, 19.2)
Hazard ratio, day 14, (95% CI)	…	Ref	0.95 (0.76, 1.20)	Ref	1.22 (0.93, 1.61)	0.91 (0.59, 1.39)	0.89 (0.58, 1.37)
Hazard ratio, day 90, (95% CI)	…	Ref	1.12 (0.95, 1.32)	Ref	1.09 (0.88, 1.35)	1.06 (0.77, 1.46)	0.80 (0.58, 1.12)
Recovery							
n	3386	1137	2249	2111	509	348	418
Median (IQR) time from admission, d	6 (3–10)	7 (4–12)	6 (3–9)	…	…	…	…
Cumulative incidence, day 28, (95% CI)[c,d]	78.6 (77.2–80.0)	71.9 (69.2–74.5)	82.0 (80.4–83.6)	…	…	…	…
Cumulative incidence, day 90, (95% CI)[d]	82.6 (81.3–83.9)	76.7 (74.2–79.2)	85.5 (84.1–87.0)	…	…	…	…
Risk ratio, day 28, (95% CI)[c,e]	…	Ref	1.40 (1.29, 1.51)	…	…	…	…
Risk ratio, day 90, (95% CI)[e]	…	Ref	1.39 (1.29, 1.50)	…	…	…	…
Sustained recovery							
n	3386	1137	2249	2111	509	348	418
Median (IQR) time from admission, d	20 (18–26)	21 (18–28)	20 (18–25)	19 (17–22)	22 (19–27)	27 (22–35)	36 (28–49)
Cumulative incidence, day 42, (95% CI)[c,d]	71.1 (69.6–72.7)	66.6 (63.8–69.3)	73.5 (71.6–75.3)	85.8 (84.3–87.3)	61.5 (57.3–65.7)	35.9 (30.9–41.0)	38.0 (33.4–42.7)

Table 2. Continued

	Total Cohort	First Wave[a]	Second Wave[b]	Respiratory Support			
				0–5 L/Minute	5–15 L/Minute	>15 L/Minute	ICU
Cumulative incidence, day 90, (95% CI)[d]	76.8 (75.4–78.2)	72.5 (69.9–75.1)	79.0 (77.3–80.7)	89.0 (87.7–90.3)	64.8 (60.7–69.0)	40.2 (35.1–45.4)	60.0 (55.4–64.7)
Risk ratio, day 42, (95% CI)[c,e]	…	Ref	1.28 (1.18, 1.39)	Ref	0.47 (0.42, 0.52)	0.22 (0.19, 0.26)	0.15 (0.13, 0.17)
Risk ratio, day 90, (95% CI)[e]	…	Ref	1.28 (1.19, 1.39)	Ref	0.46 (0.41, 0.51)	0.22 (0.19, 0.26)	0.21 (0.19, 0.23)

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; Ref, reference.

[a]Patients admitted to index admission before 15 June 2020.

[b]Patients admitted to index admission after 15 June 2020.

[c]The 42 days since index admission time point for sustained recovery and 28 days since index admission for mortality and recovery were chosen, since patients reaching sustained recovery commenced their 14-day event-free period 14 days before reaching their outcome. Therefore, day 42 in a sustained recovery outcome is timewise comparable to a day 28 mortality and recovery outcome.

[d]Death was accounted for as a competing risk.

[e]Multivariate Fine and Gray regression model.

11.5%) died after recovery, 5.4% (95% CI: 4.6–6.2%) died within the first 14 days postdischarge (Figure 1*B*). In the combined outcome, 25.8% (95% CI: 24.1–27.4%) were readmitted or died within the 90 days following discharge from the index admission (Figure 1*D*). The rates of readmission and postdischarge death were highest in the first 14 days after discharge and then leveled off to a more constant rate (Figure 1*B*–*D*, Table 2).

Recovery and Sustained Recovery

At 90 days after index admission, significantly more patients had reached the outcome of recovery than sustained recovery (Table 2, Figure 2*A*). The cumulative incidence of recovery was 78.6% (95% CI: 77.2–80.0%) at day 28 and 82.6% (95% CI: 81.3–83.9%) at day 90. The cumulative incidence of sustained recovery was 71.1% (95% CI: 69.6–72.7%) at day 42 and 76.8% (95% CI: 75.4–78.2%) at day 90 (Figure 2*A*). The median time to recovery was 6 days (IQR: 3–10 days) and median time to sustained recovery was 20 days (IQR: 18–26 days). Risk factors for failure to reach sustained recovery were older age, male sex, cardiovascular disease, diabetes mellitus, chronic pulmonary disease, renal disease, malignancies, and neurological disease (Table 3).

Outcomes by Wave

The all-cause mortality rate was lower in the second wave than the first wave (Supplementary Figure 6, Table 2). From the first to the second wave readmission rates increased but postdischarge mortality rates did not change significantly (Table 2, Supplementary Figure 6*B*). Rates of both recovery and sustained recovery were higher in the second wave compared with the first: hazard ratio of 1.39 (95% CI: 1.29–1.50) and 1.28 (95% CI: 1.19–1.39), respectively (Table 2, Supplementary Figures 4 and 7).

Outcomes by COVID-19 Disease Severity

The postdischarge mortality was substantial across subgroups defined by disease severity during the admission, except in the ICU subgroup (Table 2, Supplementary Figure 3). In a sensitivity analysis, patients were grouped by index admission duration of 14, 28, 60, and 90 days and the results were similar (data not shown).

Rates of sustained recovery decreased with increasing levels of respiratory support (Table 2, Figure 2*B*). The subgroup that received more than 15 L of oxygen had a lower cumulative incidence of sustained recovery than the ICU subgroup. We did not have access to information on clinical decisions to abstain from ICU treatment. In a sensitivity analysis we included only patients younger than 70 years of age. The exclusion of patients aged 70 years or more resulted in a significant increase in the estimates of cumulative incidence of sustained recovery among patients receiving oxygen supplementation of 5–15 L/minute or more than 15 L/minute (see Supplementary Figure 2).

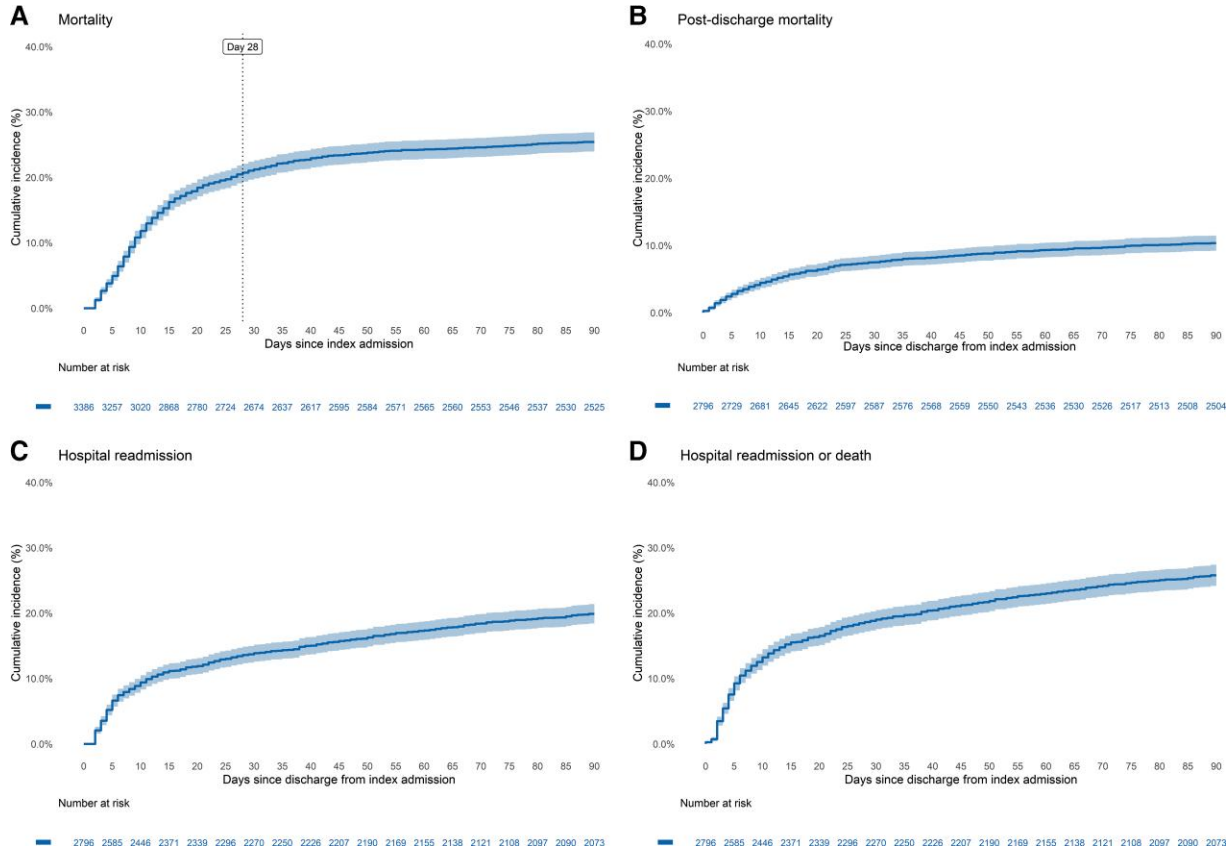

Figure 1. *A,* Cumulative incidence of death after index admission. *B,* Cumulative incidence of death after discharge from index admission. *C,* Cumulative incidence of hospital readmission after first hospital discharge from index admission. *D,* Cumulative incidence of hospital readmission or death after first hospital discharge from index admission.

Patients treated in the ICU had prolonged time to sustained recovery (median: 36 days; IQR: 28–49 days). In this subgroup, the cumulative incidence of sustained recovery increased from 38.0% (95% CI: 33.4–42.7%) at day 42 to 60.0% (95% CI: 55.4–64.7%) at day 90 after index admission (Table 2, Figure 2*B*). The relative rate of sustained recovery for the ICU group compared with the 0–5-L O_2/minute subgroup increased significantly from .15 (95% CI: .13–.17) in analyses with 42 days of follow-up to .21 (95% CI: .19–.23] with 90 days of follow-up (see Table 2 and Supplementary Figure 5).

Among patients in ICUs during the first 2 days of admission, the median time to recovery and sustained recovery was 19 (IQR: 11–33) and 36 (IQR: 26–48) days, respectively.

DISCUSSION

We examined all-cause mortality, postdischarge mortality, readmissions, recovery, and sustained recovery in a large, population-based cohort of patients admitted to a hospital with COVID-19 in eastern Denmark. Readmissions and postdischarge mortality rates were substantial and a large proportion of patients with critical illness had a protracted time to recovery.

In the total cohort, the cumulative incidence curves leveled out around day 28 for the outcome of recovery and day 42 for sustained recovery. However, among patients who received oxygen supplementation of more than 15 L O_2/minute or were admitted to the ICU during the index admission, the cumulative incidence of sustained recovery was substantially higher at day 90 compared with day 42. In adjusted analysis, comparing rates of sustained recovery between patients admitted to the ICU and patients receiving less than 5 L O_2/minute during the index admission, the risk ratio changed significantly from day 42 to day 90. These results indicate that a prolonged follow-up of 60–90 days is needed in interventional studies to assess treatment effects in critically ill patients with COVID-19.

The ACTIV-3: TICO trial reported cumulative incidence rates of sustained recovery similar to this study, although the time to sustained recovery was shorter [12]. The median age in the ACTIV-3: TICO trial was 12 years younger, which may explain part of the difference. They also reported that worse pulmonary status at baseline was associated with lower rates of sustained recovery. Our results are also in line with a meta-analysis of hospitalized patients with COVID-19 that reported a median length of stay in a hospital of 5 days, but the length of stay increased with disease severity [10]. Also, in a

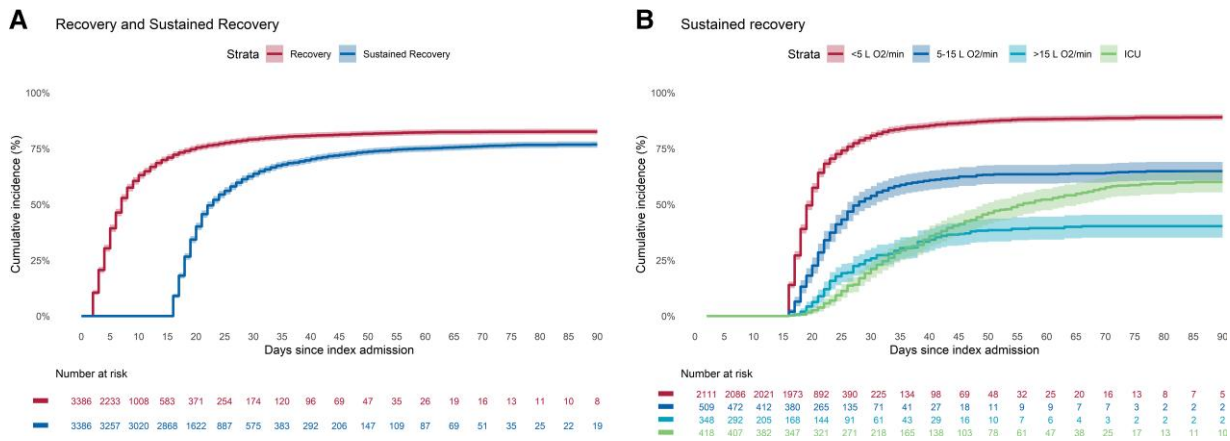

Figure 2. *A*, Cumulative incidence of recovery and sustained recovery after hospital admission. *B*, Cumulative incidence of sustained recovery stratified by the maximum level of respiratory support in the first 14 days of the admission. Abbreviation: ICU, intensive care unit.

large cohort study of 4244 critically ill patients with COVID-19, a notable proportion of patients had a protracted disease course with long hospital admission [11].

The estimates of incidence of readmissions in the present study were similar to readmission rates reported in studies from the United Kingdom and the United States, where 23% and 20% of hospitalized patients with COVID-19 had been readmitted at day 60 [1, 2]. Other studies have reported lower readmission rates. These studies have either reported on cohorts with a lower median age, with a shorter follow-up period, or with less complete rates of follow-up than this study [17–21]. Our estimates of postdischarge mortality (~10%) were similar to studies from the United States and the United Kingdom. The incidence of postdischarge mortality in the ICU subgroup was much lower than in other subgroups. Those in the ICU subgroup were younger and the prevalence of comorbidities was lower compared with other subgroups (Supplementary Table 3). In adjusted analysis comparing the ICU group with those with minimal oxygen supply the hazard ratio of postdischarge mortality was .58 but did not reach statistical significance (Table 2). Overall, we found a high incidence of postdischarge events in the first 14 days following discharge from the index admission, indicating that a 14-day postdischarge event-free period for the sustained recovery definition captures the majority of postdischarge COVID-19–associated events. A substantial number of events occurs after the initial 14 days from discharge and the event-free period in the sustained recovery definition can be prolonged (see Supplementary Table 5).

Table 3. Risk Factors for Sustained Recovery

Variables	Hazard Ratio (95% CI)	*P*
Wave		
First wave	…	…
Second wave	1.28 (1.19–1.39)	<.001
Patient age (y)		
18 to 49	…	…
50 to 69	.64 (.57–.71)	<.001
70 to 79	.49 (.43–.55)	<.001
80 to 100	.34 (.30–.39)	<.001
Sex		
Female	…	…
Male	.82 (.76–.88)	<.001
Comorbidities at baseline		
Cardiovascular disease	.87 (.79–.95)	.001
Hypertension	1.02 (.93–1.12)	.670
Diabetes mellitus	.90 (.81–.99)	.038
Chronic pulmonary disease	.84 (.76–.94)	.003
Renal disease	.67 (.56–.79)	<.001
Malignancy	.83 (.74–.94)	.003
Neurological disease	.68 (.59–.77)	<.001
Moderate/severe liver disease	.61 (.33–1.15)	.130

Abbreviation: CI, confidence interval.

From the first to the second wave, we found that rates of in-hospital mortality declined, rates of readmissions in the first 2 weeks after discharge increased, while rates of postdischarge mortality did not change significantly, resulting in higher rates of recovery and sustained recovery in the second wave than in the first wave. The introduction of remdesivir and dexamethasone as standard of care partly explains the better outcomes, but other improvements in management and treatment are also likely to have contributed. The national vaccine program started in late December 2020. Therefore, very few participants, if any, in our study would have been vaccinated prior to the index admission; further vaccination was only recommended for patients sick with COVID-19 after they had fully recovered. Thus, the availability of vaccines is not like to explain the difference.

One limitation of the study is that we could not determine if readmissions or deaths were attributable to COVID-19. A large proportion of the study population had comorbidities and thus it is likely that some of the events, especially in the last part of

the follow-up period, were unrelated to COVID-19. Data on comorbidities were obtained using diagnosis codes from prior hospital contacts and thus may be underreported. The inclusion criterion of a minimum of 48 hours' admission duration excluded patients who died earlier and could neither achieve recovery nor sustained recovery. Readmissions separated by less than 48 hours were merged, which would not affect sustained recovery due to the inherent event-free period, but may have decreased rates of postdischarge outcomes and recovery. Some patients did not have records of oxygen supply and were categorized in the lowest respiratory-support subgroup. We cannot exclude that patients may not have had all changes in respiratory support recorded in their medical records, but we do not believe that this would change the conclusions of this study. Unfortunately, we could not assess outcomes in nursing homes or similiar facilities nor long-COVID and post-COVID conditions.

Strengths of the study include the large, population-based study population and the near-complete follow-up due to the high quality of the registry data used for the study. All patients with COVID-19 in the region where the study was conducted were treated at public hospitals, with identical EHR software and a common treatment protocol. Data on deaths were collected from the Danish civil registration system, which is up to date and hence fully ascertains survival status.

We conclude that rates of adverse outcomes within 14 days after discharge of a hospital admission for COVID-19 are substantial, favoring the use of sustained recovery as the outcome as opposed to recovery in clinical COVID studies. A follow-up period of 28 days to assess outcomes in studies of treatments for COVID-19 may be too short for the critically ill.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. J. L., M. H., and K. S. M. designed the study. A. G. Z. and K. S. M. verified the raw data. J. R. oversaw the statistical analysis done by K. S. M. K. S. M. and M. H. drafted the manuscript. All authors were involved in the interpretation of results and critically reviewed the first draft and approved the final version of the manuscript. All authors had full access to all the data.

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