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ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Readmissions for Myocardial Infarction Among Survivors of COVID-19 Hospitalization

Nationwide Analysis From Pandemic Year 2020

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ABSTRACT

BACKGROUND COVID-19 is known to be associated with acute myocardial infarction (MI).

OBJECTIVES The purpose of this study was to evaluate the outcomes of 30-day readmissions for MI among survivors of COVID-19 hospitalization.

METHODS AND RESULTS We used the U.S. Nationwide Readmission Database to identify COVID-19 admissions from April 1, 2020, to November 30, 2020, using International Classification of Diseases-10th Revision-Clinical Modification (ICD-10-CM) claims. The primary outcome was 30-day readmission incidence for MI. A total of 521,251 cases of COVID-19 were included, of which 11.6% were readmitted within 30 days of discharge. The 30-day readmission incidence for MI was 0.6%. The 30-day all-cause readmission mortality incidence was 1.3%. Patients readmitted for MI were more frequently males (61.6% vs 38.4%) and had a higher Charlson comorbidity burden score (7 vs 4). The most common diagnosis among 30-day MI readmission was type 2 MI (51.1%), followed by a diagnosis of a type 1 non-ST-segment elevation MI (41.7%). ST-segment elevation MI cases constituted 7.6% of all MI-readmission whereas 0.6% of patients had unstable angina. 30-day MI readmissions with a recurrent diagnosis of COVID-19 had higher readmission mortality and incidence of complications. Conversely, the odds of performing revascularization procedures were lower for MI with recurrent COVID-19. Furthermore, MI readmissions with recurrent COVID-19 had a higher length of stay (7 vs 5 days) and cost of hospitalization ($18,398 vs $16,191) when compared with non-COVID-19 MI readmissions.

CONCLUSIONS Among survivors of COVID-19 hospitalization, 5.2% of all-cause 30-day readmissions and 12% of all-cause readmission mortality were attributed to MI. MI-related readmissions were a significant source of mortality, morbidity, and resource utilization. (JACC Adv 2023;2:100453) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting surgery

HCUP = the Healthcare Cost and Utilization Project

MI = myocardial infarction

NRD = National Readmission Database

PCI = percutaneous coronary intervention

COVID-19 is known to be associated with myocardial infarction (MI) by inducing a hypercoagulable and inflammatory response leading to unstable coronary plaques.[1-3] Myocardial injury has also been described through viral myocarditis, or indirectly stemming from hypoxemia and hemodynamic imbalances.[1,3,4] Therefore, it has been postulated that COVID-19 infection predisposes an individual to MI during the acute and recovery phase of the illness.[5-7] Inhospital MI complications with COVID-19 have been well described in the existing literature; however, data are scarce on the incidence of MI among survivors of an index COVID-19 admission. We recently evaluated types of cardiovascular readmissions following COVID-19 and reported on incidence of heart failure, stress cardiomyopathy, myocarditis, stroke, and venous thromboembolism.[8] However in that prior work, we did not examine types of MI (ie, non-ST-segment elevation myocardial infarction [NSTEMI], ST-segment elevation myocardial infarction [STEMI]), or type 1 vs type 2, and the incidence of these MI subtypes as well as revascularization procedures following discharge for COVID-19 infection has not been previously well described.

Hence in this analysis, we aimed to evaluate the incidence, outcomes, and predictors of 30-day readmissions for MI and its subtypes, among survivors of an initial COVID-19 index hospitalization in a US cohort, using the Nationwide Readmission Database (NRD) during the pandemic year 2020.

METHODS

STUDY DATA. The NRD is sponsored by the Agency for Healthcare Research and Quality and is an all-payer database that captures all admissions and readmissions in the United States, facilitating the analysis of causes for readmissions as well as resource utilization.[9] Given the deidentified nature of the database, institutional review board approval and informed consent were not required for this study.

STUDY DESIGN AND DATA SELECTION. International Classification of Diseases-10th Revision-Clinical Modification (ICD-10-CM) administrative claims was used to identify patients with COVID-19 from April 1, 2020, to November 30, 2020. The 2020 calendar year is the most currently available NRD data release. The NRD contains data on total hospital charges, which is the amount billed by the hospital. However, charges differ from the actual cost, including the total expense of hospital services. To calculate the cost, the Healthcare Cost and Utilization Project (HCUP) provides cost-to-charge ratio files that provide hospital-specific ratios or weighted average ratios to supplement the original NRD file.[9] A detailed flow chart of study methods is shown in **Figure 1**.

STUDY DEFINITIONS. Index admissions were defined as patients with a diagnosis of COVID-19 who were discharged alive from the hospital. Index admissions were identified per calendar year from April to November 2020. Since NRD cannot track cases across different years, December admissions were excluded to allow for analysis of 30-day readmission data. Readmission was defined as emergent nonelective or elective readmissions within 30 days of discharge. In patients who had multiple 30-day hospitalizations, only the first hospitalization was included in the analysis. Readmission mortality was defined as any death occurring in the hospital within 30 days of discharge from index hospitalization (excluding deaths occurring outside the hospital). Median household annual income was categorized into 4 quartiles: 0 to 25th ($1-$55,999), 26th to 50th ($56,000-$70,999), 51st to 75th ($71,000-$93,999), and 76th to 100th ($94,000+). Furthermore, 30-day MI readmission was defined as a composite of readmission for unstable angina, type 1 MI (NSTEMI or STEMI), and type 2 MI. The reason for including type 2 MI in the composite endpoint was the known overlap in diagnosis with type 1 NSTEMI in administrative datasets due to coding errors.[10] A complete list of all ICD-10 codes is given in Supplemental Table 1.

STUDY OUTCOMES. The primary outcome was 30-day readmission incidence for MI causes after index hospital discharge with COVID-19. Secondary objectives included examining the proportion of MI subtypes among MI readmission hospitalizations and evaluating the predictors of 30-day MI readmissions. An additional secondary objective was the comparison of MI readmission with vs without a recurrent COVID-19 diagnosis in terms of inhospital mortality, complications, and resource utilization (length of stay [LOS] and cost of hospitalization). We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to report the study findings (Supplemental Table 2).

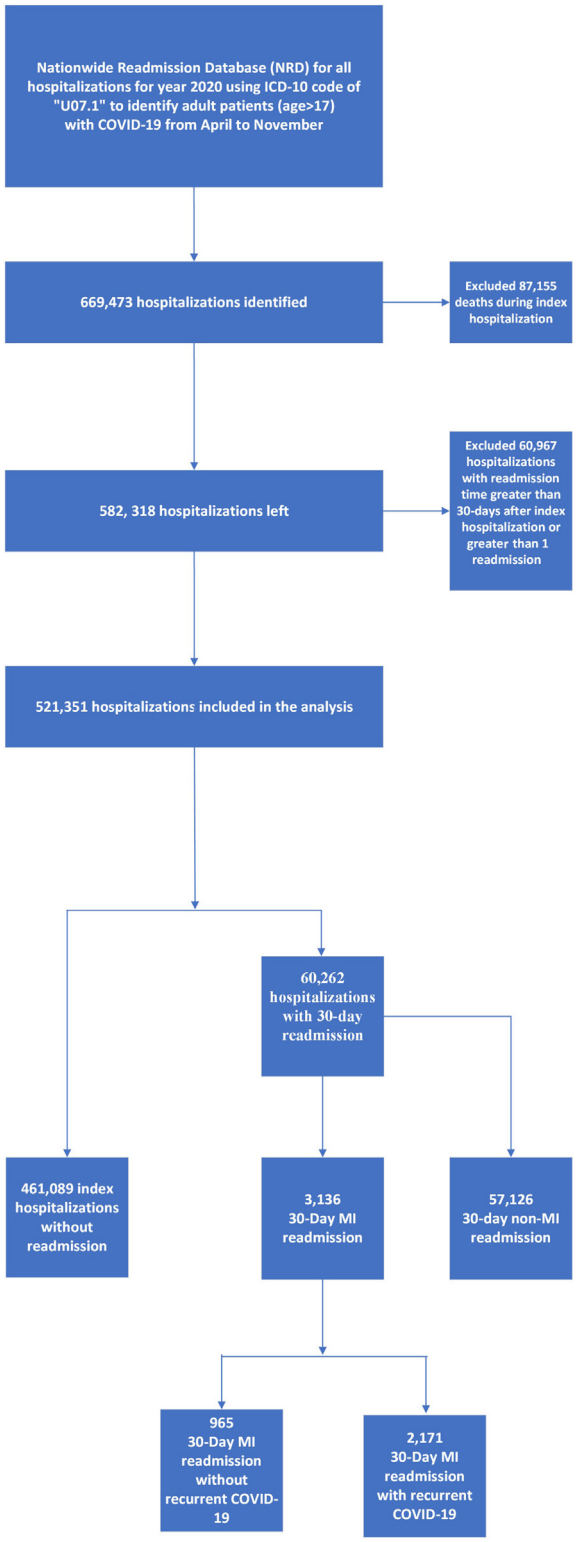
STATISTICAL ANALYSIS. All analyses were performed using nonweighted data. Categorical variables were presented as frequencies (percentage), and continuous variables were reported as median (IQR). Hospitalization characteristics were compared using Pearson chi-square and Fisher exact tests for categorical variables and Mann-Whitney *U* test and Kruskal-Wallis test for continuous variables.

A multivariable logistic regression model was developed to compute independent predictors of 30-day MI readmission. All variables were selected a priori based on their clinical relevance, which was determined by a comprehensive review of prior literature.[6,11-13] The characteristics of the index hospital stay for patients readmitted within 30 days due to a MI were compared to those initially hospitalized with COVID-19 who were not readmitted. Similarly, a comparison of index patients readmitted with MI diagnosis vs patients readmitted for non-MI causes was also performed.

Variables included in the model included demographic variables (age and sex), socioeconomic variables (median household income and insurance status), comorbidities, complications during the index admission, and medications (antiplatelet or anticoagulants). The Charlson comorbidity index was categorized at a cutoff value of 6, which was determined based on the median score of the study population. This dichotomized variable was subsequently included as a predictor in the logistic regression model. Following the removal of cases attributed to type 2 MI, a further supplementary analysis was carried out using the aforementioned multivariable logistic regression model with the aim of identifying independent predictors for 30-day readmission with MI (presumed type 1 MI). A code for statin medication was not available. NRD lacks data on race/ethnicity; hence it was not added as a variable in the model. A complete list of variables included in the model is shown in Supplemental Table 3.

We also examined whether a diagnosis code for COVID-19 was also present during the readmission hospitalization. For comparative outcomes of 30-day MI readmissions with and without a recurrent COVID-19 diagnosis, a nearest-neighbor 1:1 variable ratio, parallel, balanced propensity-matching model without replacement was made using a caliper of width equal to 0.2 of the SD of the logit of the propensity score. The balance of covariates before and after propensity score matching was assessed using the standardized mean difference. All variables to be included in the propensity matching model were selected a priori based on their clinical relevance, which was determined by a comprehensive review of prior literature.[6,11-13] R's Matchit package was used for propensity matching.[14] A complete list of variables included in the model is shown in **Table 1**. R's survival package[15] was used to compute the cumulative incidence of readmission and survivals using the log-rank test on the unmatched dataset.

FIGURE 1 Study Flow Diagram



ICD-10 = International Classification of Diseases-10th Revision; MI = myocardial infarction.

TABLE 1 Baseline Characteristics of Patients With 30-Day Myocardial Infarction Readmissions With and Without a Recurrent Diagnosis of COVID-19

	Crude Analysis			Propensity-Matched Analysis		
	MI Readmission Without COVID-19 (n = 965)	MI Readmission With COVID-19 (n = 2,171)	SMD	MI Readmission Without COVID-19 (n = 937)	MI Readmission With COVID-19 (n = 937)	SMD
Demographics						
Age, y	71 (62-80)	74 (65-82)	0.179	71 (63-81)	73 (63-82)	0.085
Age categories (y)						
≤49	74 (7.7)	124 (5.7)		70 (7.5)	61 (6.5)	
50-59	113 (11.7)	225 (10.4)		108 (11.5)	108 (11.5)	
60-69	253 (26.2)	450 (20.7)		243 (25.9)	193 (20.6)	
70-79	267 (27.7)	636 (29.3)		262 (28.0)	281 (30.0)	
≥80	258 (26.7)	736 (33.9)		254 (27.1)	294 (31.4)	
Female sex	394 (40.8)	809 (37.3)	0.073	381 (40.7)	368 (39.3)	0.028
Socioeconomic characteristics						
Primary payer			0.025			0.046
Medicare	686 (71.1)	1,624 (74.9)		667 (71.2)	697 (74.4)	
Medicaid	97 (10.1)	196 (9.0)		93 (9.9)	80 (8.5)	
Private insurance	144 (14.9)	255 (11.8)		140 (14.9)	119 (12.7)	
Self-pay	<11 (<1.1[a])	34 (1.6)		<11 (<1.2)[a]	16 (1.7)	
No charge	<11 (<1.1[a])	<11 (<0.5)[a]		<11 (<1.2)[a]	<11 (<1.2)[a]	
Others	27 (2.8)	58 (2.7)		26 (2.8)	25 (2.7)	
Missing	0 (0)	<11 (<0.5)[a]		0 (0)	0 (0)	
Median household income						
0-25th percentile	383 (40.5)	770 (35.9)	0.067	377 (40.2)	334 (35.6)	0.030
26th-50th percentile	240 (25.4)	654 (30.5)		232 (24.8)	277 (29.6)	
51st-75th percentile	193 (20.4)	452 (21.1)		186 (19.9)	194 (20.7)	
76th-100th percentile	130 (13.7)	271 (12.6)		125 (13.3)	119 (12.7)	
Missing	19 (2)	24 (1.1)		17 (1.8)	13 (1.4)	
Comorbidities						
Charlson comorbidity index	7 (6-9)	7 (6-9)	0.010	7 (6-9)	7 (6-9)	0.003
Charlson comorbidity index score >6	608 (63.0)	1,383 (63.7)		594 (63.4)	609 (65.0)	
Anemias	91 (9.4)	125 (5.8)	0.139	84 (9.0)	71 (7.6)	0.050
Hypertension	823 (85.3)	1804 (83.1)	0.060	799 (85.3)	783 (83.6)	0.047
Pre-existing heart failure	553 (57.3)	1073 (49.4)	0.158	532 (56.8)	505 (53.9)	0.058
Coronary artery disease	532 (55.1)	981 (45.2)	0.200	513 (54.7)	458 (48.9)	0.118
Cerebrovascular disease	125 (13.0)	211 (9.7)	0.102	121 (12.9)	118 (12.6)	0.010
Diabetes	545 (56.5)	1,150 (53.0)	0.070	531 (56.7)	510 (54.4)	0.045
Pulmonary hypertension	142 (14.7)	287 (13.2)	0.043	137 (14.6)	129 (13.8)	0.024
Valvular disease	71 (7.4)	123 (5.7)	0.069	66 (7.0)	64 (6.8)	0.008
Peripheral vascular disease	88 (9.1)	151 (7.0)	0.080	84 (9.0)	83 (8.9)	0.004
Obesity	188 (19.5)	409 (18.8)	0.016	179 (19.1)	165 (17.6)	0.039
Liver disease	74 (7.7)	187 (8.6)	0.035	74 (7.9)	78 (8.3)	0.016
Chronic kidney disease	448 (46.4)	1000 (46.1)	0.007	436 (46.5)	423 (45.1)	0.028
End-stage kidney disease	147 (15.2)	328 (15.1)	0.003	143 (15.3)	145 (15.5)	0.006
Prior MI	146 (15.1)	245 (11.3)	0.114	140 (14.9)	129 (13.8)	0.033
Prior PCI	119 (12.3)	212 (9.8)	0.082	119 (12.7)	93 (9.9)	0.088
Prior CABG	95 (9.8)	174 (8.0)	0.064	90 (9.6)	80 (8.5)	0.037
Pre-existing pacemaker	35 (3.6)	83 (3.8)	0.010	34 (3.6)	25 (2.7)	0.055

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Complete data were available for all variables except for primary expected payer (n = 1,022, 0.1%) and median household income (n = 5,963, 1.1%). As the overall missing values were minimal, we used listwise deletion and did not include missing values in the logistic regression analysis. All missing values are reported in the hospital characteristics **Table 1** and Supplemental Table 3.

For all analyses, a 2-tailed *P* value of 0.05 was considered statistically significant. Analyses were performed using SPSS version 27 and R software for statistical computing version 4.3.

TABLE 1 Continued

	Crude Analysis			Propensity-Matched Analysis		
	MI Readmission Without COVID-19 (n = 965)	MI Readmission With COVID-19 (n = 2,171)	SMD	MI Readmission Without COVID-19 (n = 937)	MI Readmission With COVID-19 (n = 937)	SMD
Complications during the index admission						
Pacemaker implanted during index hospitalization	<11 (<1.1[a])	<11 (<0.5)[a]	0.077	<11 (<1.2)[a]	<11 (<1.2)[a]	0.038
Atrial fibrillation	243 (25.2)	569 (26.2)	0.024	236 (25.2)	236 (25.2)	<0.001
Cardiac arrest	61 (6.3)	71 (3.3)	0.143	56 (6.0)	43 (4.6)	0.062
MI on index admission	284 (29.4)	534 (24.6)	0.109	272 (29.0)	242 (25.8)	0.072
Acute kidney injury	418 (43.3)	811 (37.4)	0.122	394 (42.0)	372 (39.7)	0.048
Cardiogenic shock	20 (2.1)	16 (0.7)	0.114	17 (1.8)	11 (1.2)	0.053
Vasopressor use	24 (2.5)	29 (1.3)	0.084	21 (2.2)	20 (2.1)	0.007
Septic shock	278 (28.8)	480 (22.1)	0.154	260 (27.7)	251 (26.8)	0.022
Mechanical ventilation	155 (16.1)	175 (8.1)	0.247	131 (14.0)	120 (12.8)	0.034
Venous thromboembolism	47 (4.9)	36 (1.7)	0.181	32 (3.4)	23 (2.5)	0.057
Mechanical circulatory support during the index admission[b]	155 (16.1)	175 (8.1)	0.101	131 (14.0)	120 (12.8)	0.059
Medications						
Current use of antiplatelets	107 (11.1)	185 (8.5)	0.086	105 (11.2)	81 (8.6)	0.086
Current use of anticoagulants	190 (19.7)	372 (17.1)	0.066	181 (19.3)	161 (17.2)	0.055

Values are median (IQR) or n (%). [a]Observations <11 are not reported per Healthcare Cost and Utilization Project guidelines. [b]Mechanical circulatory support devices included intra-aortic balloon pump, Impella, percutaneous ventricular assist device, and extracorporeal membrane oxygenation.

CABG = coronary artery bypass graft surgery; MI = myocardial Infarction; PCI = percutaneous coronary intervention; SMD = standardized mean difference.

DATA AVAILABILITY STATEMENT. NRD data are publicly available. The specific data supporting this study's findings are available from the corresponding author upon request.

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY POPULATION. A total of 521,351 patients with an index hospital admission diagnosis of COVID-19 were included in the analysis. Of the included patients, 461,089 were not readmitted and 60,262 (11.6%) were readmitted within 30 days of discharge (**Figure 1**, Supplemental Table 3). Among those readmitted, 57,126 were readmitted for a non-MI cause and 3,136 were readmitted with MI diagnoses. Thus, the incidence of 30-day readmission for MI was 0.6%, with MI-related readmissions constituting 5.2% of all readmissions. Among the survivors of the index COVID-19 admission, the 30-day readmission mortality incidence was 1.3% (n = 6,902). During the episode of readmission for MI causes, the 30-day readmission mortality incidence was 0.2% (n = 831).

Supplemental Table 3 shows the hospitalization characteristics of index COVID-19 patients with 30-day MI readmission compared with those who did not get readmitted and those with 30-day readmissions for non-MI causes. Patients with a readmission with MI had a higher median age compared with non-MI readmissions (73 vs 68 years; $P < 0.01$). MI readmissions were more frequent among male compared with female patients (61.6% vs 38.4%; $P < 0.01$). Readmissions due to MI causes occurred at a median of 6 days (IQR: 3-13 days) following index hospital discharge. The Charlson comorbidity score was higher among MI readmissions compared with patients who did not get readmitted (7 [IQR: 6-9] vs 4 [IQR: 2-6]; $P < 0.01$). Supplemental Table 4 shows additional comparison of hospitalization characteristics across subtypes of MI.

ASSOCIATION OF INDEX HOSPITALIZATION CHARACTERISTICS WITH 30-DAY MI READMISSIONS. The index hospitalization characteristics of patients with 30-day MI readmissions (n = 3,136) were compared to those who did not get readmitted (n = 461,089). Independent variables associated with 30-day MI readmission among survivors of COVID-19 index admission included: Charlson comorbidity sore >6 (OR: 3.31 [95% CI: 2.95-3.72]), anemia (OR: 1.32 [95% CI: 1.14-1.52]), pre-existing heart failure (OR: 2.14 [1.96-2.34]), coronary artery disease (OR: 1.95 [95% CI: 1.78-2.13]), pulmonary hypertension (OR: 1.90 [95% CI: 1.70-2.12]), MI on index admission (OR: 4.55 [95% CI: 4.15-4.98]), and end-stage kidney disease (OR: 2.31 [95% CI: 2.04-2.62]). In contrast, female sex (OR: 0.69 [95% CI: 0.64-0.74]), private insurance (OR: 0.83 [95% CI: 0.73-0.95]), and high median household income (OR: 0.69 [95% CI: 0.62-0.78]) were associated with lower odds of a MI

readmission within a month after discharge. A complete list of variables and their association with 30-day MI readmissions is shown in **Figure 2**.

In a supplementary analysis, we compared the 3,136 patients readmitted with MI with the 57,126 patients readmitted with non-MI causes within 30-days of initial discharge (Supplemental Figure 1). Independent variables associated with 30-day MI readmission when compared with non-MI readmissions included: Charlson comorbidity sore >6, pre-existing heart failure, coronary artery disease, MI on index admission, and end-stage kidney disease. Again, female sex and high median household income were associated with lower odds of MI readmission within a month after discharge (Supplemental Figure 1). We conducted an additional sensitivity analysis excluding type 2 MI cases, and the results were consistent with our primary analysis (Supplemental Figure 2).

CUMULATIVE INCIDENCE OF 30-DAY MI READMISSION AND 30-DAY MI READMISSION MORTALITY BY DEMOGRAPHIC VARIABLES AND SOCIOECONOMIC CHARACTERISTICS. The cumulative incidence of 30-day MI readmission was highest among patients of male sex, age ≥80 years, lower quartile of income, and with Medicare as primary insurance (**Figure 3**). Similarly, for the outcome of death during MI readmission, the survival rates were the lowest for male sex, age ≥80 years, lowest quartile of income, and Medicare insurance (P log-rank <0.01) (**Figure 4**).

READMISSION CHARACTERISTICS OF 30-DAY MI READMISSIONS BY MI SUBTYPES AND PROCEDURES PERFORMED. The most common diagnosis among 30-day MI readmission was type 2 MI (51.1%), followed by the second most common diagnosis of type 1 NSTEMI (41.7%). STEMI cases constituted 7.6% of all MI-readmission, whereas 0.6% had unstable angina (Supplemental Figure 3).

Among revascularization procedures performed during readmission hospitalization, 7.1% of patients underwent percutaneous coronary intervention (PCI) and 0.9% had coronary artery bypass grafting (CABG). Cardiogenic shock developed in 4.3% of patients with 0.8% requiring mechanical circulatory support. In terms of angiographic characteristics, the most common cause of STEMI was left anterior descending artery occlusion, followed by right coronary artery occlusion in 0.4% of cases; whereas, 0.1% had left circumflex occlusion. Mechanical complications of STEMI were seen in 0.2% of patients.

OUTCOMES OF MI READMISSIONS WITH RECURRENT COVID-19 DIAGNOSIS COMPARED WITH MI READMISSIONS WITHOUT RECURRENT COVID-19. All included patients had a diagnosis of COVID-19 on the index hospitalization. We then examined whether patients had a diagnosis of COVID-19 on the readmission hospitalization, presumed to be recurrent or relapsing COVID-19. The baseline characteristics of 30-day MI readmission for patients with and without a diagnosis of recurrent COVID-19 are shown in **Table 1**. Patients with 30-day MI readmission with a recurrent diagnosis of COVID-19 had higher readmission hospitalization mortality and incidence of acute kidney injury, acute kidney injury requiring dialysis, and the need for tracheostomy, compared to those readmitted without recurrent COVID-19. Conversely, the odds of performing revascularization procedures were lower for MI with recurrent COVID-19 (**Figure 5**, Supplemental Table 5).

We further examine subtypes of MI by presence or absence of recurrent COVID-19 diagnosis on readmission. Supplemental Tables 6 and 7 show characteristics and outcomes among patients readmitted with type 2 MI; Supplemental Tables 8 and 9 show patients with NSTEMI; and Supplemental Tables 10 and 11 show patients with STEMI. When comparing outcomes among patients with type 1 NSTEMI vs STEMI, similar results were seen with higher incidence of inhospital mortality and lower incidence of revascularization procedures in the COVID-19 MI readmission group when compared with the non-COVID-19 group (Supplemental Tables 9 and 11). Similar results were obtained with higher mortality incidence observed among MI patients with recurrent COVID-19 when compared with all-cause readmissions (Supplemental Tables 12 and 13).

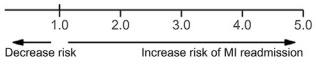
RESOURCE UTILIZATION FOR 30-DAY MI READMISSIONS. Patients with MI readmission had a median LOS of 6 days (IQR: 3-12 days) and a median hospitalization cost of $17,650 (IQR: $9,220-$36,375) compared to those readmitted without MI. When stratified by a recurrent COVID-19 diagnosis, 30-day MI readmissions with COVID-19 had a higher LOS (7 vs 5 days) and cost of hospitalization ($18,398 vs $16,191) when compared with non-COVID-19 MI readmissions (Supplemental Table 5). Similarly, STEMI admissions with a recurrent diagnosis of COVID-19 had a higher median LOS (5 vs 3 days) and cost of hospitalization when compared with the non-COVID-19 group ($25,005 vs $22,871) (Supplemental Table 8).

DISCUSSION

Our nationwide analysis of COVID-19 and 30-day MI readmissions revealed the following principal findings: MI readmissions following COVID-19 discharge accounted for 5.2% of all-cause 30-day readmissions, with MI-related readmission mortality

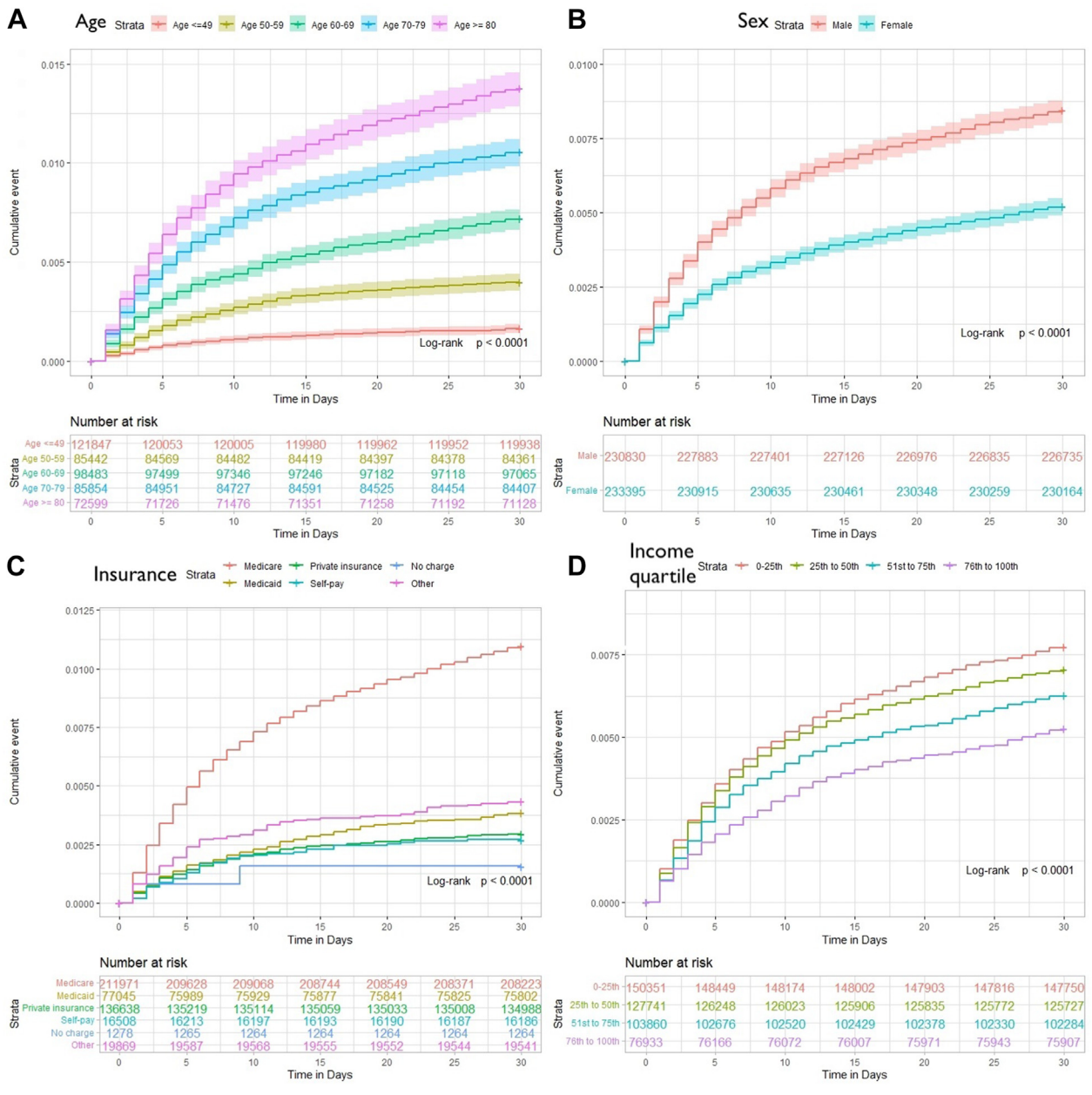
FIGURE 2 **Independent Predictors of 30-Day Readmissions With Acute MI**

Variables	Without readmission	With 30-day MI readmission	OR (95% CI)
All Patients with COVID-19	461089	3136	
Age (Categories)			
≤49 (Reference)	121649(26.4)	198(6.3)	
50-59	85104(18.5)	338(10.8)	1.62 (1.35 to 1.94)
60-69	97780(21.2)	703(22.4)	1.73 (1.45 to 2.07)
70-79	84951(18.4)	903(28.8)	1.59 (1.31 to 1.93)
80+	71605(15.5)	994(31.7)	1.50 (1.23 to 1.84)
Female sex	232192(50.4)	1203(38.4)	0.69 (0.64 to 0.74)
Socioeconomic characteristics			
Primary payer			
Medicare (Reference)	209661(45.6)	2310(73.7)	
Medicaid	76752(16.7)	293(9.4)	0.98 (0.85 to 1.13)
Private insurance	136239(29.6)	399(12.7)	0.83 (0.73 to 0.95)
Self-pay	16464(3.6)	44(1.4)	0.76 (0.55 to 1.04)
No charge	1276(0.3)	2(0.1)	0.36 (0.09 to 1.44)
Other	19784(4.3)	85(2.7)	0.84 (0.67 to 1.05)
Median houshold income			
0-25% percentile (Reference)	149198(32.7)	1153(37.3)	
26-50% percentile	126847(27.8)	894(28.9)	0.92 (0.84 to 1.01)
51-75th percentile	103215(22.6)	645(20.9)	0.86 (0.78 to 0.95)
76 to 100th percentile	76532(16.8)	401(13.0)	0.69 (0.62 to 0.78)
Comorbidities			
Charlson comorbidity index Score >6	75666(16.4)	1991(63.5)	3.31 (2.95 to 3.72)
Anemias	17846(3.9)	216(6.9)	1.32 (1.14 to 1.52)
Hypertension	284541(61.7)	2627(83.8)	1.02 (0.91 to 1.14)
Pre-existing heart failure	58129(12.6)	1626(51.8)	2.14 (1.96 to 2.34)
Coronary artery disease	65330(14.2)	1513(48.2)	1.95 (1.78 to 2.13)
Cerebrovascular disease	20593(4.5)	336(10.7)	1.09 (0.97 to 1.24)
Diabetes	173477(37.6)	1695(54.0)	1.14 (1.05 to 1.23)
Pulmonary hypertension	19963(4.3)	429(13.7)	1.90 (1.70 to 2.12)
Valvular disease	8203(1.8)	194(6.2)	1.19 (1.01 to 1.39)
Peripheral vascular disease	13766(3.0)	239(7.6)	0.99 (0.86 to 1.14)
Obesity	125446(27.2)	597(19.0)	0.81 (0.74 to 0.89)
Liver disease	19879(4.3)	261(8.3)	1.75 (1.53 to 2.01)
Chronic kidney disease	75448(16.4)	1448(46.2)	0.92 (0.83 to 1.01)
End-stage kidney disease	14134(3.1)	475(15.1)	2.31 (2.04 to 2.62)
Prior MI	15895(3.4)	391(12.5)	1.03 (0.91 to 1.16)
Prior PCI	16032(3.5)	331(10.6)	0.97 (0.85 to 1.10)
Prior CABG	12469(2.7)	269(8.6)	0.84 (0.73 to 0.97)
Preexisting pacemaker	8316(1.8)	118(3.8)	0.76 (0.63 to 0.93)
Complications during index admission			
Pacemaker implanted during index hospitalization	369(0.1)	<11(<0.4)	1.21 (0.55 to 2.66)
Atrial fibrillation	54901(11.9)	812(25.9)	0.78 (0.71 to 0.86)
Cardiac arrest	7261(1.6)	132(4.2)	0.93 (0.77 to 1.13)
MI on index admission	12928(2.8)	818(26.1)	4.55 (4.15 to 4.98)
Acute kidney injury	105190(22.8)	1229(39.2)	1.21 (1.11 to 1.31)
Cardiogenic shock	1146(0.2)	36(1.1)	0.89 (0.61 to 1.31)
Vaspressor use	5832(1.3)	53(1.7)	0.97 (0.72 to 1.31)
Septic shock	98734(21.4)	758(24.2)	0.95 (0.86 to 1.04)
Mechanical ventilation	42569(9.2)	330(10.5)	0.74 (0.65 to 0.85)
Venous thromboembolism	10089(2.2)	83(2.6)	0.80 (0.64 to 1.00)
Mechanical circulatory support	42569(9.2)	330(10.5)	2.11 (1.11 to 4.00)
Medications			
Current (long term) use of antiplatelets	13657(3.0)	292(9.3)	1.26 (1.10 to 1.43)
Current (long term) use of anticoagulants	37736(8.2)	562(17.9)	1.41 (1.27 to 1.57)



*Mechanical circulatory support devices included intra-aortic balloon pump, Impella, percutaneous ventricular assist device, and extracorporeal membrane oxygenation (ECMO). Adjusted OR is based on multivariable logistic regression model adjusted for age, sex socioeconomic characteristics, median household income, comorbidities, complications during index admissions and current (long-term) use of antiplatelets and anticoagulants. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention.

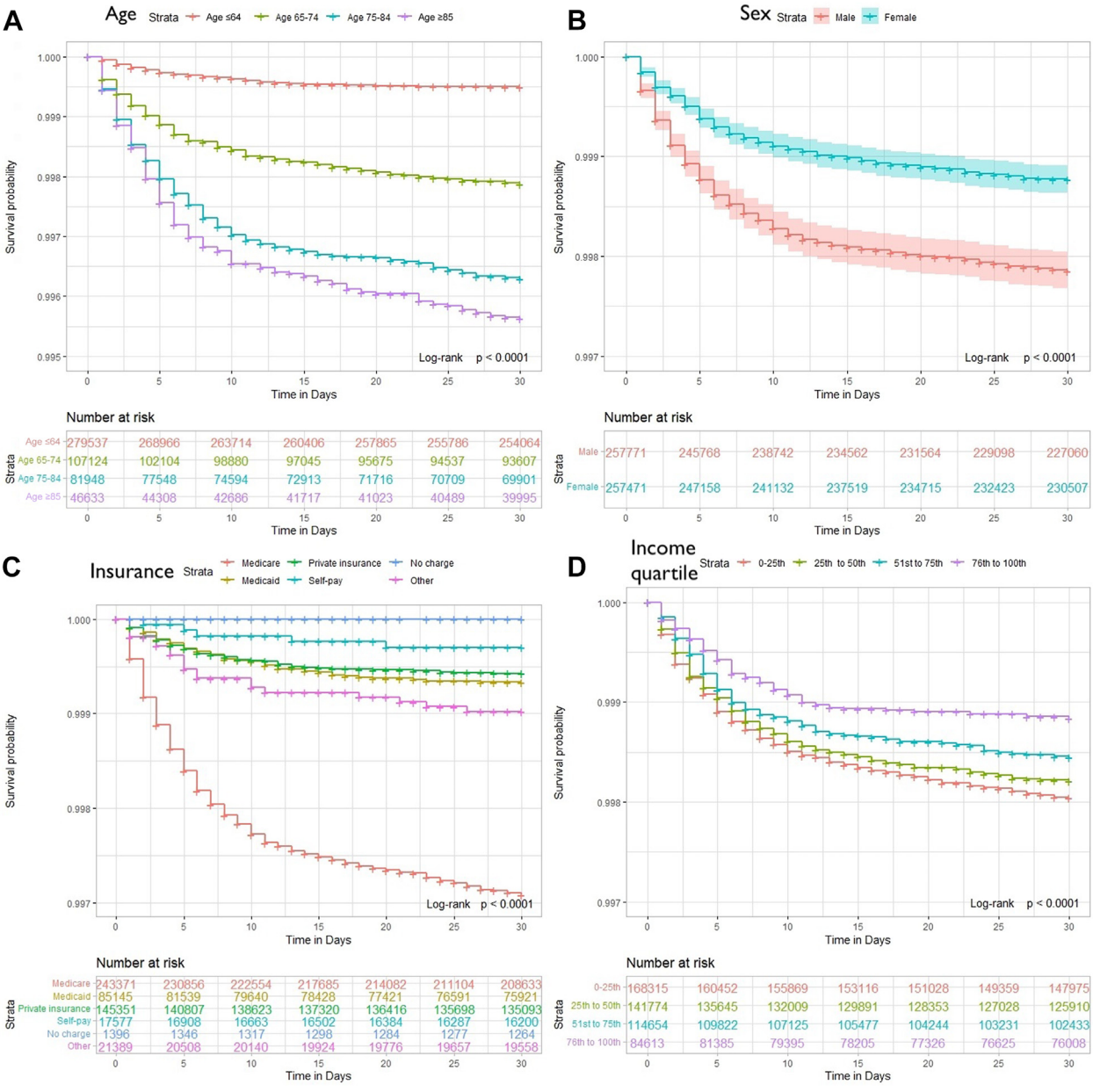
FIGURE 3 Cumulative Incidence of 30-Day Readmissions for Myocardial Infarction



(A) The cumulative incidence curve shows increased cumulative incidence of readmissions among ages >80 years compared to other age groups (*P* log-rank ≤ 0.01). **(B)** The cumulative incidence curve shows increased cumulative incidence of readmissions among male patients compared to females (*P* log-rank ≤ 0.01). **(C)** The cumulative incidence curve shows increased cumulative incidence of readmissions among patients with Medicare as their primary insurance compared to other types of insurance coverage (*P* log-rank ≤ 0.01). **(D)** The cumulative incidence curve shows increased cumulative incidence of readmissions among patients in the lowest quartile of income vs other income quartiles (*P* log-rank ≤ 0.01).

contributing to 12% of all-cause readmission mortality (**Central Illustration**). The most common MI-related readmission diagnosis was type 2 MI, followed by type 1 NSTEMI. Survivors of an initial COVID-19 hospitalization who were readmitted within 30 days with both acute MI and recurrent COVID-19 diagnosis had increased mortality and inhospital complications, and were less likely to

FIGURE 4 **Cumulative Survival Rates for 30-Day Mortality During Readmission for Myocardial Infarction**

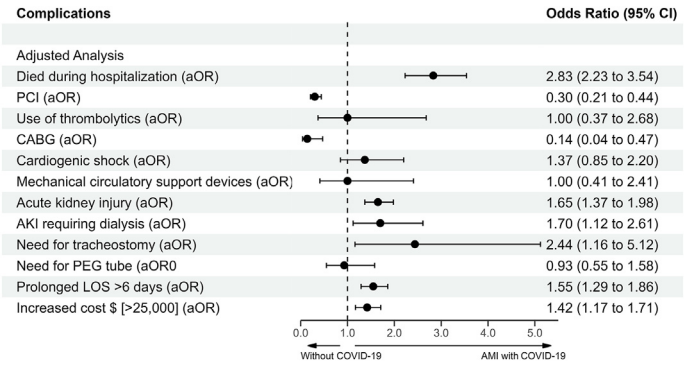


(A) Kaplan-Meier curve shows reduced survival rates among ages >80 years, compared to other age groups (*P* log-rank ≤ 0.01). **(B)** Kaplan-Meier curve shows reduced survival rates among male patients compared to females (*P* log-rank ≤ 0.01). **(C)** Kaplan-Meier curve shows reduced survival rates among patients in the lower quartile of income compared to other income groups (*P* log-rank ≤ 0.01). **(D)** Kaplan-Meier curve shows reduced survival rates among patients with Medicare as their primary insurance compared to other insurance groups (*P* log-rank ≤ 0.01).

undergo PCI than patients readmitted with MI without a recurrent COVID-19 diagnosis. MI readmissions were associated with increased resource utilization, with at-risk populations such as adults aged ≥80 years, Medicare insurance holders, and individuals belonging to lower socioeconomic groups having the highest incidence of MI readmissions and death.

MI DEFINITIONS. The fourth universal definition of MI requires evidence of myocardial ischemia (by

FIGURE 5 Adjusted Odds for Inhospital Complications for 30-Day MI Readmissions With and Without a Recurrent Diagnosis of COVID-19



Adjusted OR is based on propensity score matching model adjusted for age, sex, socioeconomic characteristics, median household income, comorbidities, complications during index admissions and current (long-term) use of antiplatelets and anticoagulants.
AKI = acute kidney injury; CABG = coronary artery bypass graft surgery; LOS = length of stay; MI = myocardial infarction; PCI = percutaneous coronary intervention; PEG = percutaneous endoscopic gastrostomy.

symptoms or electrographically) and myocardial injury with rise/fall pattern in cardiac troponin. MI is classified into 5 types, with type 1 (acute plaque rupture) and type 2 (supply-demand mismatch) being most common. Both type 1 and type 2 MIs can be STEMI or NSTEMI, but type 2 MIs are more often NSTEMI. In NRD coding, type 1 MI is classified as NSTEMI or STEMI and type 2 MI has a separate code.[16]

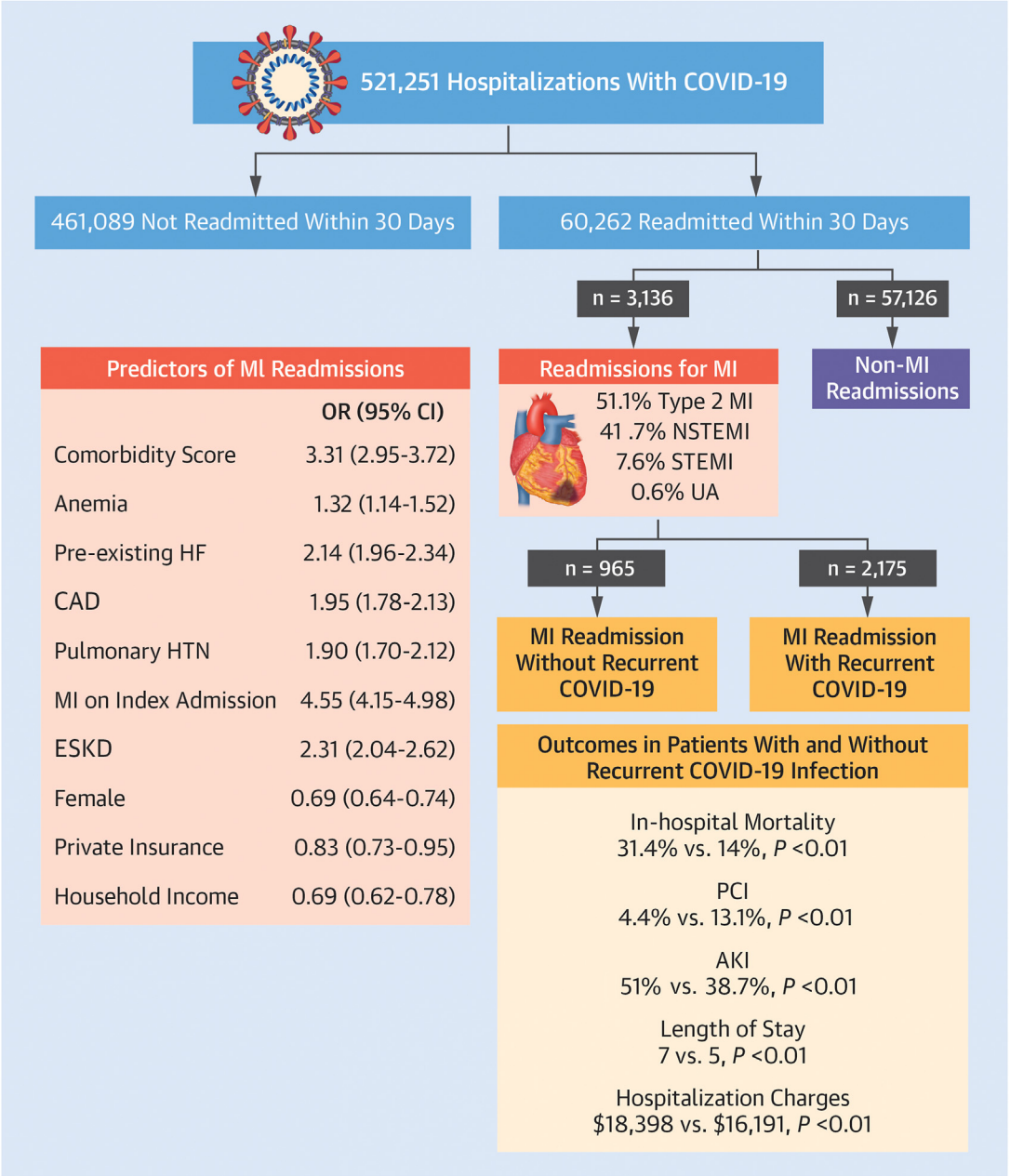
Acute COVID-19 infection increases the risk of MI during hospitalization from either type 1 or type 2 causes.[3,17] Viral infections can trigger acute plaque rupture, while severe COVID-19 can cause a type 2 MI due to various stressors.[17] While MI during the acute COVID-19 hospitalization has been described before, the incidence and characteristics of an MI occurring within 30 days following a hospitalization for COVID-19 had not been well characterized, which we now newly present in this analysis.

MI READMISSION INCIDENCE FOLLOWING DISCHARGE AFTER COVID-19 HOSPITALIZATION. COVID-19 survivors may have a higher incidence of MI due to the increased risk of thrombosis associated with the virus.[1-3] A recent study[18] has provided evidence suggesting a potential association between pneumonia and the development of myocardial fibrosis and new-onset left ventricular dysfunction, as observed through cardiac magnetic resonance imaging. It is plausible that pneumonia associated with COVID-19 could similarly contribute to the occurrence of MI by triggering an inflammatory response. Data from a recent South Korean nationwide registry of 592,719 patients showed a composite incidence of MI and strokes (occurring at 31-120 days after a diagnosis of COVID-19) of 5.49 per 1,000,000 person-days.[19] In a similar fashion, MI incidence has been shown to be higher after admission for other viral infections such as influenza.[20,21] Among patients with a diagnosed positive test for influenza, the incidence ratio for MI admission within 1 week increased to 6.05 (95% CI: 3.86-9.50).[22] Our study findings demonstrated that acute MI readmission incidence increased 1 week following discharge after COVID-19 hospitalization.

Previous studies have reported all-cause 30-day readmission incidence after COVID-19 index hospitalization to be estimated around 5% to 20%.[23-27] We recently reported that the incidence of 30-day readmission after COVID-19 for a cardiovascular cause was 5.1%, accounting for 44.3% of all-cause 30-day readmissions.[8] In this current report, we now provide national estimates for MI readmissions and MI subtypes following a COVID-19 hospitalization. Among 30-day readmissions for MI, we found that the most common diagnosis was type 2 MI (51.1%), followed by a diagnosis of type 1 NSTEMI (41.7%), while STEMI cases constituted 7.6% of all MI readmissions and 0.6% had unstable angina.

MI READMISSION COMPLICATIONS. Multiple reports from prior literature suggest that a co-diagnosis of COVID-19 is associated with worse outcomes in MI patients.[28,29] Our study further extends these findings to 30-day MI readmissions. When stratified by COVID-19 diagnosis status, patients readmitted with MI with a recurrent COVID-19 infection had significantly worse outcomes. Patients with recurrent COVID-19 and MI had lower chances of receiving PCI and CABG and higher chances of receiving thrombolytics, resulting in a 3 times higher mortality risk in cases of 30-day MI readmission with concurrent COVID-19. Note that treatment of type 2 MI is targeted toward addressing the underlying stressor and COVID-19 may act as a stressor for a type 2 MI.[3] ICD-10 codes were used to analyze NSTEMI as type 1 MI with a separate code for type 2 MI, but coding errors and overlap are possible. Lower odds of revascularization were observed in the STEMI subset population, with a 2-fold increased risk of mortality compared to matched controls without COVID-19, indicating a deviation from standard of care in STEMI management in the setting of COVID-19. These findings could be attributed to delayed presentation, delayed care, deviation from standard revascularization timing, and suboptimal care.[30] Furthermore, we postulate that

CENTRAL ILLUSTRATION **Predictors and Prognosis of 30-Day Readmissions for Acute Myocardial Infarction Among Survivors of COVID-19 Hospital Discharge**



Zahid S, et al. JACC Adv. 2023;2(6):100453.

AKI = acute kidney injury; CAD = coronary artery disease; ESKD = end stage kidney disease; HTN = hypertension; MI = myocardial infarction; NSTEMI = non-ST-segment elevation MI; PCI = Percutaneous coronary intervention; STEMI = ST-segment elevation MI.

COVID-19 may have a disease-modifying effect from ischemic damage due to the virus's inherent effect on the endothelium which leads to worse outcomes in MI patients.[4,31,32] To substantiate the claim, in our study cohort, mechanical complications occurred at an incidence of 1.3% which is higher than the expected incidence of 0.27% previously reported.[33]

The possibility exists that patients who experience readmission for COVID-19 and MI within a 30-day timeframe may have persistent viral shedding from the initial infection instead of a true COVID-19 reinfection. Unfortunately, due to the limitations inherent in the NRD claims database, it is only possible to confirm the presence of a COVID-19 diagnosis code at readmission. More granular laboratory data, such as viral PCR tests, are not available in this administrative dataset. It is plausible to hypothesize that persistent viral shedding might indicate ongoing inflammation, which could contribute to worse outcomes among patients readmitted with MI who are diagnosed again with COVID-19. Given the exploratory nature of the present findings, further investigations would be needed to elucidate the pathophysiological mechanisms underlying persistent viral shedding of COVID-19 and its potential association with worse outcomes in patients with MI.

In light of these findings, perhaps actions should be taken at the hospital infection prevention level to delabel patients who appear recovered from initial infection but are suspected of having persistent viral shedding of COVID-19, to eliminate any potential barriers to appropriate care. Additionally, cardiologists should be cognizant of the potential bias against patients flagged as COVID-19 positive, which may result in receiving suboptimal MI care. Therefore, heightened awareness and corrective measures are necessary to ensure that all patients receive equitable and optimal care regardless of their COVID-19 status.

MI-RELATED READMISSION MORTALITY. Prior studies have estimated postdischarge COVID-19-related mortality to be at 1% to 20%.[23-27] Our study found 30-day readmission mortality to be 1.3% and MI-related readmission mortality to contribute 12% to all-cause readmission mortality. Unlike previous studies, we used a representative all-comer database, increasing the strength of our findings.[24,25]

SEX DIFFERENCES AND SOCIOECONOMIC DISPARITIES. Our study reveals significant sex differences in the outcomes of MI readmissions among individuals who have survived COVID-19. Our study indicates that males face a substantially higher risk of MI readmission and subsequent mortality compared to females. These findings align with a recent study by Behrouzi et al, which also discovered that males infected with the COVID-19 were at a heightened risk of adverse outcomes within 30 days, including hospitalization for cardiovascular events, admission to the intensive care unit, the need for mechanical ventilation, or death.[34] The observed discrepancy among sexes can be attributed to a combination of genetic, immunologic, and hormonal factors, as well as distinctions that emerge in response to gender-specific behaviors.[35] To illustrate, males showcase augmented expression of the angiotensin-converting enzyme 2 receptor, thereby facilitating greater viral entry into cells, whereas females generally mount a more vigorous innate and adaptive immune response than males which results in faster clearance of pathogens.[36] Furthermore, males exhibit a greater propensity for engaging in smoking behavior, thus exacerbating the aforementioned pro-inflammatory response to virus.[37]

During the pandemic, there was a significant socioeconomic disparity observed in the outcomes of COVID-19. Our study further extends these findings to MI-related readmissions. Not only were individuals in the lower income quartiles more likely to be readmitted with MI, but also these groups were at the highest risk of dying during readmission. Our study findings warrant an urgent public health intervention with a focus on underrepresented population groups.

HEALTH CARE COST UTILIZATION. The COVID-19 pandemic proved to be a significant stressor for the health care system with an unprecedented increase in health care expenditure in many countries including the United States.[38] Though the peak of the pandemic is over with the introduction of widespread vaccination and immunity through natural infection, the economic impact of COVID-19 continues to mount.[39] We report that MI-related readmissions contribute significantly to health care expenditures. This is mainly driven by increased LOS, as well as increased morbidity such as increased incidence of chronic complication, such as requirement of dialysis and tracheostomy.

STUDY LIMITATIONS. Our study is constrained by the following limitations. First, an important limitation of the study is the possibility that competing risks may have affected the results of the survival analysis, owing to the fact that the NRD dataset used did not capture deaths or events occurring outside the hospital. As a consequence, the estimates of the probability of experiencing the event

of interest may have been biased, as some individuals who died from competing events were not accounted for in the analysis due to the lack of relevant data. Second, granular data, including vital signs, medications, inpatient treatment regimens, inhospital/out-of-hospital STEMI data, and laboratory, radiological, and echocardiographic findings, are not available. Third, NRD coding errors and variability cannot be excluded entirely. The study used ICD-10 codes instead of central adjudication for outcomes, which could result in misclassification of MI cases. The dataset had separate codes for type 1 and type 2 MI, but there could still be coding errors. The study considered both reported diagnoses of MI and found a small number of cases (<11) with overlapping MI codes, which are unlikely to affect the analysis.

Fourth, we did show that having an MI during the index COVID-19 hospitalization was associated with a diagnosis of MI on the readmission hospitalization. However, ambiguity might exist regarding whether the occurrence of type 2 MI during the 30-day readmission is an indication of ongoing biomarker elevation or a new event. The treating clinicians should have been able to deduce whether the troponin levels were declining from the prior admission by comparing the prior values from index admission with the current values on readmission. The diagnosis of MI is not made by troponin elevation alone, but by evidence of a rise/fall pattern, along with symptoms and/or electrographic evidence of ischemia. However, in this administrative dataset, we do not have access to the biomarker data or the clinical reasoning that went into the diagnosis of MI at the readmission hospitalization. Therefore, it is not possible to infer from our present analysis whether any observed biomarker elevation was persistent or an actual new event.

Fifth, though we performed multivariable logistic regression analysis and propensity matching to report adjusted estimates, residual confounding cannot be completely ruled out. Sixth, collider bias is well documented in recent observational studies evaluating COVID-19.[40,41] Though we did not restrict our study sample to any particular group and NRD provides a random sample of the US population, the introduction of bias through adjusting for variables in the logistic regression model may still exist. Seventh, our study captured outcomes during the first year of the pandemic in 2020, when vaccines were not available. Hence, we could not study outcomes stratified by vaccination status. The NRD data from years 2021 and 2022 have yet not been released; an updated examination of the incidence and causes of readmissions after COVID-19 hospitalizations should be restudied in the postvaccine era when those data are available. Finally, like any observational, retrospective study, association does not imply causation and conclusions are hypothesis-generating.

CONCLUSIONS

In our national cohort study of U.S. population during the pandemic year 2020, among survivors of index COVID-19 hospitalization, 5.2% of all 30-day readmissions and 12% of all-cause readmission mortality were attributed to MI. Type 2 MI was the most common cause of MI diagnosis followed by type 1 NSTEMI and STEMI. MI-related readmissions were a significant source of mortality, morbidity, and resource utilization. Rates of revascularization procedures like PCI and CABG were lower whereas the use of thrombolytic was higher for MI readmissions with recurrent COVID-19 compared with MI readmissions without COVID-19. The incidence of mechanical complication in STEMI patients among COVID-19 survivors was higher compared with the general population. Furthermore, the incidence of MI readmissions was the highest for vulnerable population groups belonging to lower quartiles of income as well as individuals with high comorbidity burden. Moreover, the first week after discharge was found to be the most vulnerable time for MI readmission. Though MI-related readmission may not be entirely preventable due to the presence of nonmodifiable risk factors and higher comorbidity burden, the availability of vaccination may help drive down MI-related readmissions by reducing the severity of the initial COVID-19 infection. Further studies are needed to evaluate the impact of COVID-19 vaccination on MI readmissions, mortality, and morbidity after COVID-19 infection.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Michos has advisory board participation for Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards LifeScience, Esperion, Medtronic, Novartis, Novo Nordisk, and Pfizer; is supported by the Amato Fund for Women's Cardiovascular Health research at Johns Hopkins University; and has an American Heart Association grant 946222. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: During the pandemic year 2020, 5.2% of all-cause 30-day readmissions and 12% of all-cause readmission mortality were attributed to MI following an index hospital discharge for COVID-19. Older age, higher comorbidity burden, and lower income were significant predictors of 30-day MI readmissions. The most common MI diagnosis code reported was type 2 MI followed by type 1 NSTEMI and STEMI, respectively. MI-related readmissions remain a significant source of mortality, morbidity, and resource utilization. Rates of revascularization procedures were lower, whereas the use of thrombolytic was higher for MI readmissions with a recurrent COVID-19 diagnosis compared with MI readmissions without COVID-19.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate the impact of COVID-19 vaccination on MI readmissions, mortality, and morbidity after COVID-19 infection.

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KEY WORDS CABG, COVID-19, heart failure, myocardial infarction, NSTEMI, PCI, percutaneous coronary intervention, STEMI, venous thromboembolism

APPENDIX For supplemental tables and figures, please see the online version of this paper.