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High post-discharge mortality in hospitalized COVID-19 patients with cardiovascular comorbidities

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Short title: COVID-19 post-discharge mortality and cardiovascular comorbidities

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic resulting in coronavirus disease 2019 (COVID-19) has affected more than 164 million people in more than 180 countries worldwide. Morbidity and mortality linked to COVID-19 have a significant burden on healthcare systems. The condition has also been referred to as a thrombo-inflammatory disease with exuberant inflammatory responses (hyperinflammation, cytokine storm) further resulting in uncontrolled multiorgan failure, likely a leading cause of case fatality.[1, 2]

Cardiovascular disease (CVD) is a common comorbidity in patients with COVID-19 especially in those with severe disease. More than 7% of patients experience myocardial injury from the infection (the rate is rises much higher reaching 22% in those who are critically ill).[3, 4] Studies demonstrate that COVID-19, in patients with underlying comorbidities, has an increasingly rapid and severe course. Proportions of CVD in COVID-19 patients vary substantially: 17.1% (95% CI, 13.2%–20.9%) for hypertension; 4.5% (95% CI, 3.6%–5.5%) for other CVD, and 8.5% (95% CI, 5.5%–11.4%) for diabetes mellitus.[5] Hospitalized COVID-19 patients with comorbid CVD have a poor prognosis with in-hospital mortality rates being as high as 36% in comparison to those without the history of CVD.[3-5] Notwithstanding, the information on the outcomes of the disease in these patients following hospital discharge is scarce. In this study, we report on the short-term outcomes following hospital discharge in patients with COVID-19 and CVD comorbidities.

Methods

The study conforms to the Declaration of Helsinki. Informed consent for data analysis was obtained from the patients according to the Polish law on patients’ rights regarding data
registration. Given the observational study design approval for analyzing recorded data was waived by the institutional review board on human research.

The analysis is based on the SILesian CARDiovascular (SILCARD) Database. Detailed information on the database was published previously.[6] In summary, the database comprises records from all hospitals (N= 310) in the Silesian Province. The population of the region is 4.5 million inhabitants corresponding roughly to 12% of Poland's population. The SILCARD database encompasses the information on all consecutive adult patients hospitalized in the cardiology, cardiac surgery, vascular surgery or diabetology departments for any reason, or hospitalized in the internal medicine departments or intensive care units with the principal diagnosis of cardiovascular disease (CVD). CVD was defined as any “I” code according to the 10th revision of the International Classification of Disease (ICD-10). The information on the COVID-19 hospitalizations and all-cause death was provided the National Health Fund which manages the entire health insurance system in Poland.

Altogether, the study comprised 4277 patients from the SILCARD Database hospitalized with COVID-19 between March and December 2020. The median follow-up was 72 days (47-95). Based on the patient’s status at the end of follow-up the study population was divided into two groups: Group 1: alive patients (N=2483) and Group 2: deceased patients (N=1794).

Statistical analysis

Statistical analysis was performed using STATISTICA PL version 13.3 (TIBCO, Palo Alto, USA). Quantitative data are presented as means and standard deviations (SD) or medians with interquartile ranges (lower and upper quartiles). Qualitative data are presented as frequencies. The Shapiro–Wilk test was used to determine whether random samples came from a normal distribution. The chi-square test was used to compare categorical variables. The unpaired t-test was used to compare normally-distributed continuous variables between groups. The
Mann–Whitney U-test was used to compare continuous variables with a distribution other than normal. Estimated 6-month survival curve is depicted by Kaplan-Meier method. A value of two-sided $P < 0.05$ was used to indicate statistical significance.

**Results and discussion**

1794 of 4277 patients (41.9%) with COVID-19 and CVD died during the study period. Those who died were older. Male sex, chronic coronary syndromes, heart failure, chronic kidney disease, and history of stroke were more prevalent in patients who died. Other CVD and non-CVD were also more prevalent among those patients who died (Table 1). The median length of hospital stay for alive patients at the end of follow-up was 11 (4-21) days and was longer in comparison to 10 (4-20) days for those who died during hospitalization and 10 (5-18) days for those who died after hospital discharge ($P=0.006$). However, the length of hospital stay for patients who died in the hospital was similar to the length of hospital stay for patients who died after hospital discharge ($P=0.7$). The median time to death after discharge was 14 (7-30) days.

1289 of 1794 deceased patients (71.8%) – corresponding to 30.1% of the entire study population – died during the hospital stay. By contrast, 505 of 1794 deceased patients (28.2%) – corresponding to 11.8% of the entire cohort – died after hospital discharge. Estimated 6-month post-discharge mortality rate was 21% (Supplementary material, *Figure S1*).

Cardiovascular conditions are the most frequent comorbidities in patients hospitalized with COVID-19. The rate of CVD varies from 14% to 50%.[7-9] These rates go even as high as 60% for patients in the complicated and critical phase of the disease.[7] The most frequent reported CVD include, among others, hypertension (30-56%), diabetes mellitus (15-27%), coronary artery disease (8-11%), and heart failure (7-8%).[7, 8] In our cohort of patients with CVD, the rates were substantially higher in comparison to the general population:
hypertension (69.5%), heart failure (39.6%), CAD (37.7%), diabetes mellitus (29.6%), and atrial fibrillation (AF) (15.9%). These rates correspond well with the CVD frequencies seen among COVID-19 patients with myocardial injury.[8] There is a substantial heterogeneity among studies with respect to in-hospital mortality which varies from 5% to 21%.[9] Guo et al reported that in-hospital mortality rates was linked to the presence of CVD and myocardial injury. The authors reported the mortality rates to be 7.6% in patients without underlying CVD and normal troponin T (TnT) levels, 13.3% in those with underlying CVD and normal TnT levels, 37.5% in those without underlying CVD but elevated TnT levels, and 69.4% in those with underlying CVD and elevated TnTs.[8] In-hospital mortality rate in our cohort was 16.1% and was similar to other studies. The patients hospitalized with COVID-19, after discharge still suffer with extended impact of the disease. In addition, readmission is yet another crucial indicator of disease severity and healthcare system quality. Somani et al reported that 3.6% of discharged patients returned for emergency care after just a median of 4.5 days. Respiratory distress was the most common cause for rehospitalization (50%). In addition, patients who were readmitted also had a shorter median length of stay during the index hospitalization (4.5 vs 6.7 days; \(P=0.006\)).[10] Lavery et al reported that the adjusted odds of readmission were higher for patients with specific comorbidities which included chronic obstructive pulmonary disease OR 1.35 (95%CI 1.28–1.42) \(P<0.001\); heart failure OR 1.58 (95%CI 1.48–1.67) \(P<0.001\), diabetes mellitus OR 1.21 (95%CI 1.14–1.28) \(P<0.001\), and chronic kidney disease OR 1.64 (95%CI 1.55–1.74) \(P<0.001\). The risk of hospital readmission declined with the longer length of index hospital stay OR 0.99 (95%CI 0.99–1.00) \(P=0.001\).[11] Chopra et al examined the sixty-day outcomes among hospitalized COVID-19 patients.[12] The authors demonstrated that 398 (24.2%) died during hospitalization. By 60 days after discharge, additional 84 patients (17.4% of those who died; 5.0% of the entire study cohort) had died. This has resulted in an overall mortality rate for the
cohort to reach 29.2%.[12] We report a much higher post-discharge mortality rate among patients with comorbid CVD accounting for roughly 28.2% of all deceased COVID-19 patients (11.8% of the entire study population). In our study, the median time to death after discharge was 14 (7-30) days. Overall mortality rate in our cohort of COVID-19 patients with CVDs reached 41.9%.

Owing to the reported post-discharge readmission and mortality rates, there seem to be an urgent need for creating practice guidelines for safe discharge. In particular, endeavors should be undertaken for CVD patients who might appear stable at discharge with regard to the acuity and location of care continuance. A designed managed care programs for discharged COVID-19 patients should include close monitoring (telemedicine), scheduled out-patient cardiology visits and planned rehabilitation programs. These actions might prevent hospital readmission rates and improve prognosis. This managed care strategies should be particularly intensive within 1-2 months of discharge.

**Study limitations**

The results of the study should be considered in light of its limitations. First, the SILCARD registry is based on the electronic database of a single, national insurance company and is limited to core variables, such as demographic data, co-morbidities, in-hospital and follow-up events. In addition, the quality of data may be affected by the discordance between the quality of information reported by various centers. And finally, many of these discharges took place in the earlier period of the COVID-19 pandemic when there were no clear management recommendations.
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Table 1. Baseline and clinical features of the studied populations

|                          | All patients (N=4277) | Alive patients (N=2483) | Deceased patients (N=1794) | P     |
|--------------------------|-----------------------|-------------------------|-----------------------------|-------|
| Mean age, years (standard deviation) | 72 (12)               | 69 (13)                 | 75 (10)                     | <0.001|
| Women, N (%)             | 1851 (43.3)           | 1131 (45.5)             | 720 (40.1)                  | <0.001|
| Chronic coronary syndromes, N (%) | 1947 (45.5)         | 1075 (43.3)             | 872 (48.6)                  | 0.001 |
| History of myocardial infarction, N (%) | 483 (11.3)           | 259 (10.4)              | 224 (12.5)                  | 0.041 |
| Heart failure, N (%)     | 1528 (35.7)           | 717 (28.9)              | 811 (45.2)                  | <0.001|
| Hypertension, N (%)      | 3153 (73.7)           | 1798 (72.4)             | 1355 (75.5)                 | 0.024 |
| Diabetes mellitus, N (%) | 1629 (38.1)           | 867 (34.9)              | 762 (42.5)                  | <0.001|
| Atrial fibrillation, N (%) | 922 (21.6)           | 497 (20.0)              | 425 (23.7)                  | 0.004 |
| Arrhythmias (excl. atrial fibrillation), N (%) | 881 (20.6)           | 520 (20.9)              | 361 (20.1)                  | 0.53  |
| History of stroke, N (%) | 740 (17.3)            | 384 (15.6)              | 356 (19.8)                  | <0.001|
| Prior PCI, N (%)         | 456 (10.7)            | 243 (9.8)               | 213 (11.9)                  | 0.033 |
| Prior CABG, N (%)        | 69 (1.6)              | 45 (1.8)                | 24 (1.3)                    | 0.27  |
| COPD, N (%)              | 537 (12.6)            | 282 (11.4)              | 255 (14.2)                  | 0.006 |
| Asthma, N (%)            | 460 (10.8)            | 269 (10.8)              | 191 (10.6)                  | 0.88  |
| CKD stage 3 or higher, N (%) | 669 (15.6)           | 309 (12.4)              | 360 (20.1)                  | <0.001|
| Renal replacement therapy, N (%) | 155 (3.6)            | 80 (3.2)                | 75 (4.2)                    | 0.11  |
| Cancer, N (%)*           | 1276 (29.8)           | 723 (29.1)              | 553 (30.8)                  | 0.18  |

CABG – coronary artery bypass surgery; CKD – chronic kidney disease; CRT-D – implantable cardiac resynchronization therapy defibrillator; COPD – chronic obstructive pulmonary disease; ICD – implantable cardioverter-defibrillator; PCI – percutaneous coronary intervention

*History of or current cancer