Original Article

Cardiac complications of COVID-19: Incidence and outcomes

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A B S T R A C T

Background: Coronavirus disease-2019 (COVID-19) has been associated with pre-existing cardiac conditions as well as cardiovascular complications. The incidence rates of cardiac complications, age, and gender differences in this population are unknown.

Objectives: We wanted to study the incidence of cardiac complications and mortality in patients with COVID-19.

Methods: Data from the TriNetX COVID-19 global research network platform was used to identify COVID-19 patients. We compared patients with and without cardiac complications in patients with COVID-19 and obtained survival data.

Results: The final cohort was composed of 81,844 patients with COVID-19. Cardiac complications occurred in 9.3% of patients as follows: acute coronary syndromes in 1.3%, heart failure in 4.4%, atrial fibrillation in 4.5%, sinus bradycardia 1.9%, ventricular tachycardia in 0.5% and complete heart block in 0.01%. Mortality was significantly higher in patients with the cardiac complications mentioned (20%) than in those without them (2.9%) (odds ratio 7.2, 95% CI, 6.7–7.7; p < 0.0001). Older males seem to have higher incidence of cardiac complications and mortality.

Conclusions: Patients with COVID-19 who have cardiac complications have a higher risk of mortality when compared to those without cardiac complications.

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1. Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged from Wuhan, China at the turn of 2019 and has spread rapidly across the world resulting in the Coronavirus Disease 2019 (COVID-19) pandemic.1-2 It is a single-stranded RNA virus and is closely related to the same genus of Corona viruses that caused Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome-Coronavirus (MERS-CoV).3 To date, the virus has affected more than 450 million people leading to more than 6 million deaths worldwide.1 The virus has caused significant morbidity, mortality, and economic consequences throughout the world. With over 24 months into the pandemic, there is evolving evidence regarding complications and late outcomes.4-6

The SARS-CoV-2 virus typically causes respiratory symptoms that can progress to respiratory failure requiring ventilation and lead to pulmonary complications.7 Other organ systems such as the cardiovascular system are also affected. Studies have shown greater prevalence of hypertension, diabetes, and ischemic heart disease in hospitalized COVID-19 patients who are acutely ill; and mortality is higher in patients with pre-existing cardiovascular conditions.8 Several published case reports and small studies have emerged that described heart failure, myocarditis, acute myocardial injury, and atrial fibrillation associated with COVID-19, but their prevalence in a real world COVID-19 population is unknown.9-12 A small single center study reported a 19% incidence of cardiac injury in COVID-19 patients with associated higher mortality, but cardiac injury was not defined explicitly in terms of specific cardiac complications.13 Another recent study reported the arrhythmic complications in hospitalized COVID-19 patients; however, it was a single center study only.14

Thus, we sought to study the incidence and prevalence of cardiac complications in COVID-19 patients. Specifically, we aimed to study the incidence of heart failure, atrial fibrillation, ventricular tachycardia, complete heart block, and acute coronary syndromes.
We sought to examine patients who experienced cardiac complications with COVID-19 and compared mortality to those without cardiac complications.

2. Methods

Data was obtained from TriNetX (Cambridge, MA, USA) which is a global research network platform that continuously obtains de-identified clinical data from participating health care organizations (HCO). Recently, they created the TriNetX COVID-19 Research Network platform to facilitate research related to COVID-19. It contains electronic medical record data from 44 health care organizations representing hospitals, academic medical centers, and primary care/specialty centers across the world, including our institution. As of July 31st 2020, TriNetX housed data of more than 60 million patients and provided access to continuously updated, de-identified aggregate data. It has a waiver from Western Institutional Review Board since only aggregated counts and statistical summaries of de-identified information, without protected health information, are received. TriNetX features allow real-time access to de-identified longitudinal clinical data along with analytics to study the research questions.

The current study included data of all COVID-19 patients at US and international centers of the TriNetX COVID-19 Research Network as of July 31st, 2020. COVID-19 patients were defined as those with a COVID-19 diagnosis code (ICD-10 codes: B34.2, B97.29, J12.81, U07.1, U07.2) since January 20, 2020. We excluded patients with diagnosis codes of other specified viral infections (ICD-9 code: 079.89) during the same timeframe. Patients with cardiac complications were obtained based on ICD-9 and ICD-10 codes for acute coronary syndrome (ACS) (I20, I21, I21.01, I21.02, I21.1, I21.09, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I21.4, I22, I22.9), atrial fibrillation (AF) (I48, I48.0, I48.1, I48.11, I48.19, I48.2, I48.20, I48.21, I48.9, I48.91), heart failure (HF) (I50, I50.1, I50.2, I50.20, I50.21, I50.22, I50.23, I50.3, I50.30, I50.31, I50.32, I50.33, I50.4, I50.81, I50.82, I50.84, I50.9, I11), myocarditis (I40, I51.4, I40.9, B33.22), cardiogenic shock (R57.0), third degree complete heart block (CHB (I44.2), sinus brady-cardia (R00.1, I49.5, I49.8), and ventricular tachycardia (VT) (I47.2, I49.02, I49). The above diagnosis codes that we queried for cardiac complications include acute heart failure, persistent AF, permanent AF, and chronic AF. We also noted the incidence of pulmonary embolism but did not include it in the cohort of cardiac complications. We recorded the reported use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) in this population.

The database allows to query for ICD-9/10 diagnosis codes for a specific event or outcome over a specific period of time. The first incidence of the event, most recent occurrence, and prevalence at any time prior to or after the event specified can be queried. As such, we obtained patients with a diagnosis of COVID-19 and queried for cardiac complications that occurred after the diagnosis.

We grouped patients into two cohorts: those with cardiac complications and those without cardiac complications. Demographic data, diagnoses, medications, labs, procedures performed, hospitalization, and specified outcomes within each group were compared. We also assessed the proportion of patients on ACEI/ARB medications in each group. Total number of deaths after the diagnosis of COVID-19 were obtained. A 1:1 propensity matching for all the demographics and comorbidities (age, gender, ethnicity, COPD, CAD, HTN, DM, CKD, CVA, obesity, EF, and cardiovascular medications including beta blockers, ACEI, and ARB) were performed and Kaplan Meier survival curves were obtained after matching. Lastly, we compared patients with cardiac complications who died versus those who survived within the group.

Our data came primarily from US HCOs. International sites comprised 20% of HCOs and included sites in Europe, Middle East, Africa, Brazil, and South Korea. For a specified outcome, there was variability in the number of HCOs from which the data was obtained. The proportions of HCOs from which data could be obtained are listed.

2.1. Statistical analysis

All statistical analyses were conducted on the TriNetX platform, which utilizes a combination of JAVA™, R, and Python™ programming languages. Descriptive statistics were obtained for all study variables. All categorical variables were compared for the study outcome by using the Fisher exact test or χ2 test; Continuous variables were compared using the t statistic. Continuous data are expressed as mean and standard deviation. Categorical data are expressed as percentages. Survival curves were plotted using the Kaplan–Meier method for patients with vs. without cardiac complications before and after propensity matching using the log-rank test. For all the statistical analyses, p < 0.05 was considered significant. Differences in demographics and co-morbidities between survivors and non survivors were obtained; however multivariate analysis for predictors could not be conducted on the platform.

3. Results

The total cohort size consisted of 81,844 patients who had a diagnosis of COVID-19 obtained from 40 out of the 44 healthcare organizations with 15% from non-US sites. Table 1 demonstrates baseline characteristics for these patients. Table 2 shows the baseline characteristics of COVID-19 patients with and without cardiac complications both with and without propensity matching. Between January 20th, 2020 and July 31st 2020, 21% of these patients required hospital services including critical care. Mortality rate was 5% (n = 4014). Mean age of those who died was 73 ± 14 years.

Among the COVID-19 patients, 9.3% (n = 7682) of patients developed cardiac complications after diagnosis of COVID-19. Non-US sites contributed to 11% of the data. In fact, 6.3% (n = 5914) of patients developed for the first time a new cardiac diagnosis (de novo). The mean age of patients who developed cardiac complications with COVID-19 and compared mortality to those without cardiac complications.
complications was higher at 68 ± 17 years with 55% male. Patients reported symptoms of syncope (5%), palpitations (3%), tachycardia (17%), dyspnea (40%), bradycardia (17%), cough (24%), fever (23%), and fatigue (24%) over this time period and mean troponin elevation was 12 ± 57 ng/mL (0–0.4 ng/mL).

Atrial Fibrillation was the most common (4.5%, n = 3702), followed by heart failure (4.4%, n = 3624) (Fig. 1). Cardiogenic shock occurred in 0.3% (n = 263) of patients. Myocarditis was a discharge diagnosis in at least 10 of these patients. Complete heart block occurred in a minority (n = 10) of patients. ACS occurred in 1.3% (n = 1093) of patients. VT developed in 0.5% (n = 399) of patients. Sinus bradycardia occurred in 1.9% (n = 1595).

Fig. 2a shows the distribution of de novo cardiac events (i.e. these events occurred for the first time without prior history). Fig. 2b shows the distribution of new events and those with a recurrence. Heart failure was the most common complication that occurred in 2216 patients as new onset HF. Acute systolic heart failure occurred in 1771 patients (2%) of which 234 patients sustained cardiogenic shock. One hundred and thirty-three patients were diagnosed with right heart failure. New onset right heart failure was observed in 108 of the 138 patients. Pulmonary embolism (PE) occurred in 984 patients after COVID-19 diagnosis of which 720 cases were de novo. Acute right heart failure from acute PE occurred in 10 patients. Four hundred and fifty-eight patients developed pulmonary hypertension after COVID-19 diagnosis. New onset AF and ACS occurred in 1970 and 878 patients respectively. Two hundred ninety-one patients had VT.

Table 2
Baseline characteristics of patients with and without cardiac complications: Unmatched and propensity matched cohorts.

| Variables                        | COVID patients with cardiac complications (7,682) | Non-cardiac COVID patients (7,4162) | p-value | Propensity matched Cardiac COVID patients (n = 7594) | Propensity matched Non cardiac COVID patients (n = 7594) | p-value |
|----------------------------------|--------------------------------------------------|-------------------------------------|---------|-----------------------------------------------------|-------------------------------------------------------|---------|
| Age (years ± SD)*                | 68 ± 17.5                                         | 47.6 ± 20.2                         | <0.001  | 66.8 ± 17.7                                         | 66.6 ± 17.5                                           | 0.6     |
| Gender (Male) (%)                | 55                                               | 44                                  | <0.0001 | 54                                                  | 55                                                   | 0.5     |
| DM (%)                           | 38                                               | 12                                  | 0.001   | 36                                                  | 35                                                   | 0.6     |
| HTN (%)                          | 67                                               | 24                                  | <0.001  | 64                                                  | 65                                                   | 0.8     |
| CVA (%)                          | 23                                               | 5                                   | <0.001  | 20                                                  | 20                                                   | 0.9     |
| CAD (%)                          | 39                                               | 6                                   | <0.001  | 35                                                  | 34                                                   | 0.1     |
| Overweight and Obesity (BMI > 25) (%) | 29                                               | 15                                  | <0.001  | 27                                                  | 26                                                   | 0.05    |
| COPD (%)                         | 20                                               | 3                                   | <0.001  | 17.6                                               | 16.2                                                 | 0.1     |
| EF (%) ± SDa                     | 55.1 ± 14.7                                       | 60.4 ± 10.6                         | <0.001  | 54.2 ± 15.7                                         | 55.8 ± 16                                             | 0.02    |
| CKD (%)                          | 30                                               | 5                                   | <0.0001 | 27                                                  | 26                                                   | 0.5     |
| ACE inhibitors (%)               | 35                                               | 11                                  | <0.001  | 32.7                                               | 31.3                                                 | 0.6     |
| ARB II (%)                       | 25                                               | 7                                   | <0.001  | 23                                                  | 22                                                   | 0.2     |
| Beta-blockers (%)                | 56                                               | 15                                  | <0.001  | 53                                                  | 52                                                   | 0.4     |

* EF was stratified as < 50% and >50%. *Age was stratified into two deciles (every 20 years).

Incidence of cardiac Complications of COVID-19.

Shown are the rates of various cardiac complications occurring in patients with COVID-19 with Heart failure and Atrial fibrillation contributing to the majority of complications.

Fig. 1. Incidence of cardiac Complications of COVID-19.
Medical treatment consisted of beta blockers in 43%, diuretics in 42%, ACE inhibitors in 12%, ARBs in 11%, amiodarone in 9%, antiplatelet inhibitors in 31%, and statins in 34%. Alteplase was given in 5% and cardiac catheterization procedures were performed in 10%. Only 1% (n = 90) of patients underwent cardiac catheterization with coronary stenting performed in 13 patients. Nineteen percent of patients received azithromycin. Hydroxychloroquine was used in 15% and Lopinavir-ritonavir was used in 1%. Glucocorticoids, which included prednisolone, methylprednisolone, dexamethasone and hydrocortisone, were used in 35% of patients. Critical care services were required in 24% of these patients. Four percent required ventilation and 2% were on hemodialysis.

Death was observed in 20% (n = 1541) of patients with cardiac complications. This rate was higher than the death rate in patients without cardiac complications (2.9%) [Odds ratio = 7.2 (6.7–7.7), p < 0.0001]. Patients with cardiac complications were older, more likely to be male, and had a greater number of comorbidities (Table 2b). After propensity matching, mortality was still higher in the groups with cardiac complications than the group without cardiac complications, with an odds ratio of 2.29 (17% vs. 8%) (CI 2.07–2.5, p < 0.001). Fig. 4b shows the Kaplan–Meier survival curves of the two groups after propensity matching for all the characteristics (log rank p-value < 0.001).

Patients with cardiac complications who died were older and more commonly male compared to those who survived and had a higher percentage of comorbidities. There was no difference in ACE inhibitors and ARB usage among survivors and those who died (Table 3).

4. Discussion

Our study revealed that cardiac complications occurred in 9.3% of COVID-19 patients with a mortality of 20% in those with cardiac events. This mortality rate is nearly seven times higher than the...
2.9% mortality of COVID-19 population without cardiac events. Heart failure and atrial fibrillation were the most common cardiac complications observed in our cohort.

**Fig. 3.** Number of Health Care Organizations from which data is obtained.

**Fig. 4.** b. Propensity Matched Kaplan-Meier survival curves for patients with and without cardiac complications.
This is the first larger scale study describing cardiac event rates in a large COVID-19 patient cohort. Currently, there are several smaller studies reporting extra-pulmonary cardiac complications of SARS-CoV2 infection\(^5,7,16\) but this is the first study of this magnitude.

The incidence of heart failure (4.6%) in our analysis was lower compared to the study by Zhou et al which reported acute heart failure in 23% of 191 hospitalized patients with COVID-19 in Wuhan\(^7\). This discrepancy may be due to the fact that Zhou et al included all hospitalized inpatients who were much sicker compared to the all-comers outpatient and inpatient population included in our study. Thus large studies like our current study, help in discerning the true incidence of cardiac events. Acute PE contributing to acute right heart failure occurred only in a minority of patients and did not seem to contaminate the sample of cardiogenic shock patients in our cohort. It is well known that viruses are an etiology of acute myocarditis. Small case reports suggested an association between COVID-19 and myocarditis.\(^18\) Cardiac MRI demonstrated myocardial edema and injury in these patients. A prospective observational study showed myocardial inflammation by CMR in 60% of patients recently recovered from COVID-19 infection.\(^25\) Thus we planned to examine the rate of myocarditis diagnoses in our dataset. However myocarditis was identified in only 10 patients because only one HCO contributed this diagnosis to the dataset (Fig. 3). The true incidence of myocarditis may be higher and could not be determined in our dataset.

The etiology of cardiac complications in COVID-19 is probably multifactorial. Microvascular and microvascular thrombi have been described, with D-dimer elevation correlating with severity of illness and mortality.\(^20,21\) The hypercoagulable state may directly be related to the risk of acute coronary syndrome. The hypercoagulable state may reflect the inflammatory cytokine response, as noted with increased inflammatory cytokines,\(^22-23\) and could play an important role in cardiac complications like myocarditis, atrial fibrillation, and ensuing heart failure.

Cardiac arrhythmias are also commonly noted in COVID-19 patients. A small study of 138 COVID-19 patients from Wuhan\(^7\) noted an incidence of 16.7% arrhythmias in their cohort. However, the authors did not describe if these were supraventricular or ventricular arrhythmias. The incidence of AF and VT in our study was 4.5% and 0.5%, respectively. AF seems to be the most common arrhythmia in COVID-19 population.\(^24\) The recent single center study by Bhatla et al reports incident AF as 3.6% that is in line with our study. Clinically significant bradycardia was 1.2% in their cohort.\(^24\) In our study as well, the incidence of CHB was low while sinus bradycardia was relatively frequent and occurred in 2% of the population. Episodes of CHB and sinus bradycardia have been described in other studies as well (24). We excluded sinus tachycardia in our cardiac events cohort as it is a dynamic event and could be affected by fever, medications, and other extrinsic factors.

Prior small studies from China and Italy showed that patients with advanced age, underlying comorbidities, and pre-existing cardiovascular disease were at risk for severe clinical course.\(^25-28\) Along similar lines, our study also shows that older patients and those with comorbidities like diabetes mellitus, hypertension, and coronary artery disease had a higher incidence of cardiac complications. Older males have previously been identified as a significant risk group overall as well for severe COVID-19 and death.\(^28,29\) To date, there has been no multicenter study that defined the incidence of all cardiac complications after SARS-CoV2 infection. While women had a higher incidence of COVID-19, cardiac events and mortality occurred more frequently in men in our study.

There has been considerable debate on the risks and benefits of using ACEi and angiotensin receptor blockers in COVID-19. SARS-CoV2 virus enters the cell by attaching to the ACE-2 receptor, subsequently leading to viral replication.\(^26,31\) It has been postulated that upregulation of ACE-2 receptors with ACE inhibitors/ARB use could potentially increase viral entry into cells.\(^32\) However, single center and population-based studies demonstrated no evidence of ACE inhibitors/ARBs increasing the risk of COVID-19 or disease severity.\(^33,34\) Our analysis yielded a similar trend: the use of ACE inhibitors/ARB was not associated with mortality in COVID-19 patients who had cardiac complications.

Several studies reported myocardial injury and increased mortality with troponin elevation.\(^31,35,36\) Troponin elevation was noted in 6% of hospitalized patients in Turkey.\(^37\) Since our study included outliers and inpatients, the incidence of troponin elevation was lower (1.3%) but again troponin was higher in the group of patients that died. Regardless it should be noted that the incidence of AF and heart failure is much higher than the incidence of ACS in the our COVID-19 population. After our study was undertaken, several other studies were also published and various cardiac outcomes as reported are listed (Table 4).

### 4.1. Limitations

Our study has several limitations. First, this is a retrospective study with data obtained from querying diagnostic and procedure codes from EMRs, and hence it is subject to data reporting bias and missing data bias. Hence, we were also unable to analyze symptoms based on severity of COVID-19. Second, we were limited in our statistical analysis due to the platform. TriNetX provides its own

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**Table 3**

| Variables | Survivors (n = 6130) | Deceased (n = 1541) | p-value |
|-----------|----------------------|---------------------|---------|
| Age (years) | 66.5 ± 18 | 74 ± 13.6 | <0.0001 |
| Gender (Male) | 53.8 (3299) | 60.6 (935) | <0.0001 |
| DM (%) | 37.5 (2303) | 48.4 (746) | <0.0001 |
| HTN (%) | 66.7 (4091) | 79.2 (1221) | <0.0001 |
| CVA (%) | 11.3 (698) | 15.8 (245) | <0.0001 |
| CAD (%) | 35.5 (2178) | 42.3 (652) | <0.0001 |
| BMI | 31 ± 9 | 29 ± 8 | 0.001 |
| COPD (%) | 19.6 (1206) | 25.7 (397) | <0.0001 |
| EF (%) | 53 ± 12 | 52 ± 16 | 0.02 |
| CKD (%) | 28.9 (1773) | 43.6 (673) | <0.0001 |
| ACE (%) | 34.5 (2118) | 38.2 (589) | 0.07 |
| ARB II (%) | 25.4 (1559) | 24.4 (377) | 0.4 |
| BB (%) | 56.5 (3464) | 65.3 (1007) | <0.0001 |
| Serum Creatinine (mg/dl) | 1.6 ± 3 | 2.1 ± 2 | <0.0001 |
| BNP (pg/ml) | 414 ± 877 | 630 ± 976 | <0.0001 |
| Troponin (ng/ml) | 9 ± 45 | 23 ± 84 | <0.0001 |
statistical analysis of the large data, making multivariate analysis limited. Therefore, we were unable to conduct a stratified multi-variate analysis. Third, we were unable to clearly establish deaths limited. Therefore, we were unable to conduct a stratified statistical analysis of the large data, making multivariate analysis.

5. Conclusions

Cardiac complications were observed in approximately 10% of COVID-19 patients in our preliminary study. When cardiac complications do occur, patients have a higher mortality as compared with patients without cardiac complications. Further research is needed to study these cardiac complications in COVID-19, as they have prognostic and management implications.

6. Key points

1. Cardiac complications occurred in 10% of Covid-19 population inclusive of inpatient and outpatient setting

2. When cardiac complications do occur, patients have a higher mortality as compared with patients without cardiac complications

Disclosures

The above authors have no relevant conflicts of interest to disclose.

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