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ORIGINAL ARTICLE

Cardiac Complications in Patients Hospitalised With COVID-19 in Australia

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Objectives	Describe the incidence of cardiac complications in patients admitted to hospital with COVID-19 in Australia.
Design	Observational cohort study.
Setting	Twenty-one (21) Australian hospitals.
Participants	Consecutive patients aged ≥18 years admitted to hospital with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
Main outcome measures	Incidence of cardiac complications.

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Trial registration: AUS-COVID. ACTRN12620000486921. http://www.anzctr.org.au/.

Results Six-hundred-and-forty-four (644) hospitalised patients (62.5±20.1 yo, 51.1% male) with COVID-19 were enrolled in the study. Overall in-hospital mortality was 14.3%. Twenty (20) (3.6%) patients developed new atrial fibrillation or flutter during admission and 9 (1.6%) patients were diagnosed with new heart failure or cardiomyopathy. Three (3) (0.5%) patients developed high grade atrioventricular (AV) block. Two (2) (0.3%) patients were clinically diagnosed with pericarditis or myopericarditis. Among the 295 (45.8%) patients with at least one troponin measurement, 99 (33.6%) had a peak troponin above the upper limit of normal (ULN). In-hospital mortality was higher in patients with raised troponin (32.3% vs 6.1%, $p<0.001$). New onset atrial fibrillation or flutter (6.4% vs 1.0%, $p=0.001$) and troponin elevation above the ULN (50.3% vs 16.4%, $p<0.001$) were more common in patients 65 years and older. There was no significant difference in the rate of cardiac complications between males and females.

Conclusions Among patients with COVID-19 requiring hospitalisation in Australia, troponin elevation was common but clinical cardiac sequelae were uncommon. The incidence of atrial arrhythmias and troponin elevation was greatest in patients 65 years and older.

Keywords COVID-19 • Cardiomyopathy • Arrhythmia • Troponin

Introduction

Originating in Wuhan, China in late 2019, coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread globally at a rapid pace and was declared a pandemic by March 2020 [1]. Due to the surge in cases, health care systems around the world were inundated with highly infectious patients, placing an unprecedented strain on hospital resources. The World Health Organisation has reported over 200 million cumulative cases and over four million deaths globally as of August 2021 [2]. Australia, however, benefitting from geographical isolation as well as prompt border closures and enforcement of strict social distancing laws, has experienced a relatively low number of cases [3]. Consequently hospitals in Australia have not been overwhelmed and have not had to limit the provision of care to elderly and frail patients. Hence, Australia provides a unique and important opportunity to study the outcomes of hospitalised patients with COVID-19.

SARS-CoV-2 infection has a wide spectrum of clinical manifestations ranging from asymptomatic to multisystem involvement and death [4]. Of interest, early data from small case series suggested that cardiac complications such as acute cardiac injury, myocarditis and cardiomyopathy were common in patients with COVID-19 [5,6]. Despite these early signals, there are few high quality studies that systematically report cardiac complications of COVID-19. The available data, moreover, is largely extracted from small or highly selective cohorts in a pandemic setting which have an unclear comparability to the population of Australia. The aim of our multicentre study, conducted in the context of a health care system that has not been overwhelmed, is to provide an unbiased representation of the incidence of clinical cardiac complications in hospitalised patients infected with SARS-CoV-2.

Methods

Trial Oversight

The Australian Cardiovascular COVID-19 Registry (AUS-COVID) captures data from 21 hospitals in four Australian states (Appendix Table 1). The study protocol is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12620000486921). A waiver of consent was granted by the Northern Sydney Local Health District Human Research Ethics Committee (HREC 2020/ETH00732).

Patients

The registry includes all consecutive index hospitalisations with laboratory proven SARS-CoV-2 infection. All consecutive patients aged 18 years or older are included in the registry. All consecutive patients entered in the AUS-COVID Registry by 28 January 2021 were included in the present study. Key exclusion criteria are patients with suspected but not laboratory proven SARS-CoV-2 infection. Given that many of the included sites are major tertiary cardiac centres, patients transferred from another hospital are also excluded to avoid recruitment bias.

Outcomes

The demographic characteristics, baseline comorbidities, admission medications, investigation results, treatments and outcomes data were extracted retrospectively from electronic and paper medical records by trained research personnel using a standardised data collection form. The primary outcome was the incidence of cardiac complications, which was defined as new onset atrial fibrillation or flutter, high-grade atrioventricular block, Torsades de pointes, new or worsening heart failure or cardiomyopathy, pericarditis or myocarditis and troponin elevation above the reference range for the assay used. Pre-existing coronary artery disease

was defined as prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, angina or greater than 50% stenosis of an epicardial vessel on coronary angiography. Other comorbidities were based on the documented medical history available from electronic and paper medical records.

Statistical Analysis

Categorical variables were reported as frequencies and percentages, and continuous variables as means and standard deviations. Pearson's Chi-square test and Fisher's exact test were used to compare proportions between groups for categorical variables when expected cell sizes were ≥ 5 and <5 respectively. Results were considered significantly different if the two-sided p-value was <0.05. Statistical analysis was performed using IBM SPSS Statistics Subscription (Version 1.0.0.1508).

Results

Six-hundred-and-forty-four (644) consecutive patients from 21 hospitals across Australia with SARS-CoV-2 infection were enrolled in the study. The mean age on admission was 62.5 (±20.1) years. Three-hundred-and-twenty-nine (329) (51.1%) patients were male, 107 (15.7%) were nursing home residents and 41 (6.4%) were health care workers (Table 1).

Baseline comorbidity data were available for 612 (95.0%) patients. The most common comorbidity was hypertension which was present in 307 (50.2%) patients. One-hundred-and-eighty (180) (29.4%) patients had hypercholesterolaemia, 161 (26.3%) had diabetes mellitus, 69 (11.3%) had coronary artery disease, 59 (9.6%) had atrial fibrillation or flutter, 40 (6.5%) had heart failure or cardiomyopathy.

Data describing admission medication use were available for 582 (90.4%) patients. 189 (32.5%) were on a statin, 121 (20.8%) were on an angiotensin receptor blocker, 88 (15.1%) were on an angiotensin converting enzyme inhibitor, 92 (15.8%) were on a beta blocker, 93 (16.0%) were on aspirin, and 21 (3.6%) were on a P2Y12 inhibitor. Of the patients, 44 (7.6%) were on a direct oral anticoagulant and 10 (1.7%) were on warfarin.

Outcomes

One-hundred-and-twenty-five (125) (19.4%) patients were admitted to the intensive care unit and 70 (10.9%) required intubation. Ninety-two (92) (14.3%) died in hospital. Fifteen (15) (2.3%) patients were transferred to another hospital and their final outcome was not known.

Arrhythmias

Twenty (20) (3.6%) patients developed new atrial fibrillation or flutter during admission. One (1) patient underwent a direct current cardioversion which successfully restored sinus rhythm.

Table 1 Baseline demographics and comorbidities on admission.

Demographics	**N=644**
Mean age (SD) - yr	62.5 (20.1)
Male – no. (%)	329 (51.1)
Health care worker – no. (%)	41 (6.4)
Nursing home resident – no. (%)	107 (15.7)
Comorbidities	**N=612**
Hypertension – no (%)	307 (50.2)
Coronary artery disease – no. (%)	69 (11.3)
Heart failure or cardiomyopathy – no. (%)	40 (6.5)
Atrial fibrillation or flutter – no. (%)	59 (9.6)
PPM/ICD – no. (%)	24 (3.9)
Severe valvular disease – no. (%)	15 (2.5)
Stroke or TIA – no. (%)	48 (7.8)
Hypercholesterolaemia – no. (%)	180 (29.4)
Diabetes mellitus – no. (%)	161 (26.3)
Peripheral arterial disease – no. (%)	7 (1.1)
Current or recent smoker (<1 yr) – no. (%)	26 (4.2)
Chronic obstructive pulmonary disease – no. (%)	50 (8.2)
Asthma – no. (%)	71 (11.6)
Chronic kidney disease (eGFR < 60 mL/min/1.73m^2) – no. (%)	50 (8.2)
Medications	**N=582**
ACE inhibitor – no. (%)	88 (15.1)
ARB or ARNI – no. (%)	121 (20.8)
Mineralcorticoid receptor antagonist – no. (%)	19 (3.3)
Loop diuretic – no. (%)	69 (11.9)
Thiazide diuretic – no. (%)	41 (7.0)
Beta blocker – no. (%)	92 (15.8)
Non-dihydropyridine calcium channel blocker – no. (%)	7 (1.2)
Dihydropyridine calcium channel blocker – no. (%)	94 (16.2)
Digoxin – no. (%)	9 (1.5)
Flecainide – no. (%)	6 (1.0)
Amiodarone – no. (%)	5 (0.9)
Statin	189 (32.5)
Ezetimibe	18 (3.1)
Aspirin	93 (16.0)
P2Y12 inhibitor	21 (3.6)
Direct oral anticoagulant – no. (%)	44 (7.6)
Warfarin – no. (%)	10 (1.7)

Abbreviations: PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor.

Among patients admitted without a baseline permanent pacemaker or implantable cardioverter defibrillator, three (0.5%) developed high grade atrioventricular (AV) block (one had Mobitz II AV block and two had third degree AV block). All three patients survived to discharge. One (1) (0.2%) underwent implantation of a dual chamber permanent pacemaker prior to discharge.

No patient developed Torsades de pointes. Overall, hydroxychloroquine and azithromycin were used in 20 (3.1%) and 222 (34.5%) patients respectively. Notably, only 16 (2.5%) patients received both of these QTc prolonging medications.

Heart Failure or Cardiomyopathy

Nine (9) (1.6%) patients were diagnosed with new heart failure or cardiomyopathy. Of these nine patients, six patients had an echocardiogram and four had a left ventricular ejection fraction (LVEF) <50% with one patient reported as having mild left ventricular (LV) impairment with no ejection fraction provided, while the other had an elevated B-type natriuretic peptide (BNP). The other three patients were clinically diagnosed with heart failure and did not have an echocardiogram, BNP or NT-proBNP. No patient was diagnosed with Takotsubo cardiomyopathy. Eight (8) of the nine patients with new onset heart failure or cardiomyopathy had a high-sensitivity troponin measured and in all cases the peak troponin was above the upper limit of normal (ULN). Six (6) had a high-sensitivity troponin more than five times the upper limit of normal. Five (5) (55.6%) of these nine patients with new onset heart failure or cardiomyopathy died.

Of the 40 patients with a previous diagnosis of heart failure or cardiomyopathy, 12 (30.0%) patients were clinically assessed to have worsening heart failure or cardiomyopathy. None of these patients underwent an echocardiogram. Six (6) patients had a BNP or NT-proBNP measured, four of which were significantly elevated (BNP>500 ng/L, NT-proBNP>1,800 ng/L). Seven (7) (58.3%) of the 12 died.

Pericarditis and Myocarditis

Two (2) (0.3%) patients were clinically diagnosed with pericarditis. One (1) patient had a normal troponin, whilst the other had a mildly elevated troponin (<5×ULN), raising the possibility of myopericarditis. Neither patient had an echocardiogram, cardiac MRI or biopsy. Both patients survived to discharge.

Troponin Elevation

Out of the 644 patients included in this study, 295 (45.8%) patients had at least one troponin measurement during their admission for a clinical indication. Ninety-nine (99) (33.6%) had a peak troponin above the ULN, of which the peak troponin was greater than five times the ULN in 40 patients. In-hospital mortality was higher in patients with a troponin above the ULN (32.3% vs 6.1%, p<0.001). Mortality amongst patients with mild (>1 to ≤5×ULN) and severe (>5×ULN) troponin elevations was 27.1% (n=16) and 40.0% (n=16), respectively.

Only 16 patients (16.2%) with a troponin above the ULN had an echocardiogram, and of these only two (12.5%) demonstrated a regional wall motion abnormality. No patient with a troponin above the ULN underwent an inpatient invasive coronary angiogram, computed tomography coronary angiogram or a cardiac stress test.

One patient had a troponin rise and ST-segment elevation on electrocardiogram but was deemed not suitable for coronary angiography or thrombolysis and subsequently died.

Complications by Subgroups

The incidence rates of cardiac complications by baseline characteristics are presented in Table 2. New onset atrial fibrillation or flutter (6.4% vs 1.0%, p=0.001) and elevated troponins above the ULN (50.3% vs 16.4%, p<0.001) were more common in patients 65 years and older. There was no significant difference in the incidence of cardiac complications between males and females on univariable analysis.

Discussion

In this multicentre Australian study of over 600 consecutive patients admitted to hospital with COVID-19 the incidence of clinical cardiac complications during index hospitalisation in patients without prior cardiac history was low. Prior history of heart failure and age >65 increased the risk of cardiac sequelae.

Arrhythmias

The rate of new atrial fibrillation or flutter was 3.6% in our study. This is lower than other similar studies of hospitalised patients published earlier in the pandemic. In an Italian study of 414 patients (mean age 66.9±15.0 years), 12.1% of patients developed new atrial fibrillation or flutter [7]. In an American study of 1,053 consecutive hospitalised patients (mean age 62±17 years), 9.6% of patients developed new atrial fibrillation or flutter [8] compared to 3.6% in our study. While the mean age of the patients in these studies was similar to that in our cohort, the mortality rates (25.8% and 17.5% respectively) as well as the prevalence of baseline cardiovascular comorbidities were higher in these studies. Therefore, the excess incidence of atrial fibrillation presented may be a reflection of an overall sicker population of COVID-19 patients in these countries when compared to that of Australia.

High grade AV block was uncommon in our study (0.5%). These results are consistent with two smaller studies from Italy and China [9,10].

Torsades de pointes was not observed in our study. Notably very few patients received both the QTc prolonging medications hydroxychloroquine and azithromycin together. Our results are consistent with findings from recent systematic reviews and meta-analysis which report rates of 0.4% and 0.06% [11,12].

Table 2 Cardiac complications by baseline characteristics.

	n/N (%)								
	New Atrial Fibrillation or Flutter			New Heart Failure or Cardiomyopathy			Troponin Above the ULN		
All patients	20/553 (3.6)			9/572 (1.6)			99/295 (33.6)		
Subgroups									
Baseline Characteristic	**Yes**	**No**	**P-value**	**Yes**	**No**	**P-value**	**Yes**	**No**	**P-value**
Age ≥65 yr	17/265 (6.4)	3/288 (1.0)	0.001	7/284 (2.5)	2/288 (0.7)	0.105	75/149 (50.3)	24/146 (16.4)	<0.001
Male	10/275 (3.6)	10/268 (3.7)	0.980	6/286 (2.1)	3/286 (1.0)	0.504	52/155 (33.5)	46/130 (35.4)	0.745
Nursing home resident	2/81 (2.5)	18/472 (3.8)	0.753	1/76 (1.3)	8/496 (1.6)	1.000	14/20 (70.0)	84/265 (31.7)	0.001
Hypertension	10/259 (3.9)	10/294 (3.4)	0.773	4/277 (1.4)	5/295 (1.7)	1.000	63/143 (44.1)	35/142 (24.6)	0.001
Hypercholesterolaemia	5/158 (3.2)	15/395 (3.8)	0.719	3/165 (1.8)	6/407 (1.5)	0.722	33/82 (40.2)	65/203 (32.0)	0.186
Diabetes mellitus	6/148 (4.1)	14/405 (3.5)	0.739	1/151 (0.7)	8/421 (1.9)	0.457	31/75 (41.3)	67/143 (31.9)	0.140
Coronary artery disease	3/56 (5.4)	17/497 (3.4)	0.443	1/52 (1.9)	8/520 (1.5)	0.579	22/36 (61.1)	76/249 (30.5)	<0.001
Atrial fibrillation or flutter	-	-	-	1/44 (2.3)	8/528 (1.5)	0.516	20/27 (74.1)	78/258 (30.2)	<0.001
Chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2)	1/35 (2.9)	19/518 (3.7)	1.000	1/37 (2.7)	8/535 (1.5)	0.455	18/25 (72.0)	80/260 (30.8)	<0.001
Heart failure or cardiomyopathy	0/25 (0)	20/528 (3.8)	1.000	-	-	-	15/19 (78.9)	83/266 (31.2)	<0.001
Stroke or transient ischaemic attack	3/35 (8.6)	17/518 (3.3)	0.126	0/37 (0)	9/535 (1.7)	1.000	12/18 (66.7)	86/267 (32.2)	0.003
Chronic pulmonary obstructive disease	1/38 (2.6)	19/515 (3.7)	1.000	1/38 (2.6)	8/534 (1.5)	0.464	16/27 (59.3)	82/258 (31.8)	0.004
Asthma	2/64 (3.1)	18/489 (3.7)	1.000	0/68 (0)	9/504 (1.8)	0.608	8/32 (25.0)	90/253 (35.6)	0.235

Heart Failure or Cardiomyopathy

Previous studies have reported a high rate of cardiomyopathy and heart failure secondary to COVID-19. However, these studies have been either on small or highly selective cohorts, with high mortality rates, which has limited their generalisability. For instance, Arentz *et al.* (2020) reported 33% of patients developed a new cardiomyopathy however this was in a small sample of 21 patients admitted to an intensive care unit [6]. In a study of 850 hospitalised patients in New York, 2.8% developed new heart failure during hospitalisation [13]. The mortality rate in this study was again notably high at 22.2% (n=189). In the present study, amongst the 572 patients without a pre-existing diagnosis of heart failure or cardiomyopathy, mortality was 12.4% and only 1.6% patients were diagnosed as having new heart failure or cardiomyopathy. It is important to note that all these studies, including ours, possibly under report the true rates of new and worsening pre-existing cardiomyopathy given that echocardiography was not routinely performed on all patients.

Pericarditis and Myopericarditis

Acute myopericarditis has been recognised as a possible complication of COVID-19 in case reports. However, little is known about its incidence. A systematic review found only a total of 12 cases of confirmed myocarditis in the literature, in which the diagnosis was confirmed with cardiac magnetic resonance imaging (MRI) (Lake Louise consensus criteria) or histopathology [14]. In our present study of the 644 patients, only 2 (0.31%) were clinically diagnosed with pericarditis or myopericarditis. However, our study may have underreported the true incidence of myopericarditis given that cardiac MRI was rarely performed and the fact that myopericarditis may be a delayed complication of COVID-19 that did not manifest during the index hospitalisation.

Troponin Elevation

The high incidence of myocardial injury as demonstrated by elevated troponins above the ULN in our study is consistent with previous studies. The troponin was above the ULN in 33.6% of patients that had a troponin measured in our study. In a single centre cohort study of 416 consecutive patients (median age 64 years) admitted to hospital with COVID-19, 19.7% of patients had a high-sensitivity troponin I (hs-TNI) above the 99th percentile [15]. In a large multicentre study of 6,247 patients hospitalised with COVID-19, 29% had a troponin above the 99th percentile upper reference limit (URL) within the first 48 hours of admission [16]. The study

also demonstrated that mild (1-3×URL) and severe (>3×URL) troponin elevations were associated with an increased odds ratio for mortality of 2.06 (95% CI, 1.68–2.53; p<0.001) and 4.51 (95% CI, 3.66–5.54; p<0.001), respectively. The cause of troponin elevation, however, remains poorly understood. It is hypothesised that the troponin elevation in COVID-19 may be secondary to cytokines, microangiopathy, myocarditis or oxygen supply demand mismatch [17]. While these mechanisms likely represent the majority of cases, it should be noted that acute plaque rupture in the setting of respiratory illness is a well recognised phenomenon and has been reported in COVID-19 [10]. Given that no patient in our study underwent coronary angiography, we were unable to distinguish patients who had plaque rupture as a cause of their troponin rise. However, the lack of ST-segment elevation in all but one patient suggests that true epicardial coronary occlusion is less likely to be a common phenomenon.

Comparison to Influenza

It is interesting to consider how the incidence rate of cardiac complications with SARS-CoV-2 compares to influenza. In a large multicentre study of patients hospitalised with influenza in the United States, 6.2% of patients had an episode of acute heart failure, although this study included patients with pre-existing chronic heart failure and cardiomyopathy [18]. In a single centre series of 123 hospitalised patients with H1N1 influenza, six (4.9%) patients had new or worsening LV cardiomyopathy on echocardiography [19]. With regards to atrial fibrillation, observational studies have suggested the prevalence of atrial fibrillation in hospitalised patients with influenza ranges from 7.9–15.8%, however these studies have included patients with known atrial fibrillation [20,21]. In relation to acute cardiac injury, two large studies in the United States demonstrated that troponin elevation occurred in 2.9–5.2% of patients with influenza, however these results should be interpreted with caution as the criteria for measuring troponins varies widely [22,23]. Taken together, these findings suggest that apart from troponin rise, the incidence of cardiac complications in patients with SARS-CoV-2 and influenza infections are comparable, although once again, broad variability in outcome reporting limits the strength of this conclusion.

Limitations

This study reports on clinical complications during index hospitalisation only. Investigations were all based on clinical indication. It is possible that patients had subclinical complications which would only have been captured if systematic investigations, such as echocardiography and cardiac MRI, were performed in all patients. Moreover, data on patient outcomes after discharge from hospital have not been captured and cardiac complications such as myopericarditis or heart failure may manifest weeks after discharge. Future studies should be designed to address these limitations. Nevertheless, to the best of our knowledge, this study is the first to comprehensively capture and report the cardiovascular complications of COVID-19 in a health care system that was not overwhelmed by the COVID-19 pandemic.

Conclusion

This study provides clarification on the incidence of cardiac complications in hospitalised COVID-19 patients, utilising a large, multicentre registry in the landscape of a health care system that has not been be overwhelmed by COVID-19. While troponin elevation is common, the incidence of other cardiac complications is low and these complications are especially uncommon in those under the age of 65.

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Conflicts of Interest

There are no conflicts of interest to disclose.

Appendices. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2021.08.001.

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