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Low incidence of cardiac complications from COVID-19 and its treatment among hospitalised patients in Singapore

Dear Editor,

The COVID-19 outbreak in Singapore largely occurred among migrant workers within dormitories, while community transmission remained low. As such, the overall demographic of COVID-19 infections in Singapore disproportionately involved younger patients without significant past medical history.[1] We sought to investigate the electrocardiographic manifestations and cardiovascular complications observed in hospitalised COVID-19 patients.

This study examined a retrospective cohort of 554 consecutive patients with confirmed COVID-19 diagnosis (on nasopharyngeal swab polymerase chain reaction on the Roche cobas platform) from 23 January 2020 to 30 April 2020. Clinical background and laboratory findings were collected retrospectively. All patients also underwent a standard 12-lead surface electrocardiography (ECG). A prolonged QTc was defined as >450ms in men and >470ms in women.[2] Clinical outcomes in terms of patients who required intensive care, mechanical ventilation and other adverse events such as myocarditis/myocardial injury and death were tabulated. Ethics approval was obtained (NHG DSRB 2020/00545) from the institutional review board with a waiver of informed consent.

The study population was divided based on the presence of chest pain and the presence of pneumonia, which was used as a surrogate measure of disease severity. To compare the groups, one-way analysis of variance (ANOVA) was used for continuous parameters, while categorical parameters were compared by Kruskal-Wallis and chi-square tests for association. All statistical tests were performed using SPSS Statistics software version 25 (IBM Corp, Armonk, US) where a *P* value of <0.05 was considered statistically significant.

There were 57 (10.3%) patients with pneumonia, 19 (3.4%) requiring intensive care, and 2 (0.4%) deaths related to respiratory complications. Isolated chest pain was present in 28 (5.1%) patients. Only 1 (5.0%) case had a prior history of ischaemic heart disease, who was also the only patient with chest pain to develop a significant elevation in troponin-I (hs-TnI) levels. Patients with more severe illness with pneumonia were more likely to have had an elevated troponin level but these patients often did not have corresponding chest pain. On ECG, T-wave inversions (TWI) and ectopic beats (either atrial or ventricular) were more commonly seen in patients with chest pain. The most common location of pain was central but both left and right sided chest pain were observed as well. Of the 28 patients who developed chest pain, 18 (64.3%) were characterised to be atypical chest pain while 4 (14.3%) had non-cardiac musculoskeletal chest pain, and 6 (21.4%) had typical chest pain (Table 1).

The most common ECG finding was sinus rhythm (n=391, 64.3%). Sinus bradycardia was seen in 77 (28.6%) and sinus tachycardia was seen in 52 (7.1%) of those with chest pain. For the entire study population, 1 (0.2%) case of new-onset atrial fibrillation was observed. A prolonged QTc (88/554, 15.9%) at presentation was observed in some patients, and these patients tended to be older, and with cardiovascular risk factors. Prolonged QTc was associated with pneumonia, acute kidney injury, and requiring mechanical ventilation or intensive care. A widened QRS complex was also observed (14/554, 2.5%) in some patients. This predominantly manifested as a right bundle branch block (RBBB) or interventricular conduction delay (IVCD) while no cases of left bundle branch block were observed. Treatment with lopinavir/ritonavir (20.3% versus 6.6%, $P<0.001$) and remdesivir (16.4% vs 2.3%, $P<0.001$) appeared to be associated with prolonged QTc, while treatment with lopinavir/ritonavir appears associated with a widened QRS (30.8% vs 8.0%, $P=0.004$), but not remdesivir or hydroxychloroquine.

Chest pain has been reported as a presenting symptom in COVID-19. Cardiac injury as evidenced by elevated serum levels of hs-TnI, abnormalities of electrocardiograms or cardiac ultrasounds has been reported in 7.2–22% of patients.[3] There may be direct cardiac injury via unstable plaque rupture, thrombosis, demand ischaemia or myocarditis.[4-6] Differentiating these mechanisms in COVID-19 remains challenging. In our experience of mostly younger patients with low cardiac risk, chest pain was relatively uncommon, and none of these patients had chest pain as their sole presenting symptom. Several patients had chest pain with corresponding T-wave inversions on ECG but without a significant rise in hs-TnI. Unfortunately, further cardiac stress testing could not be obtained as patients defaulted follow-up. We speculate that these patients could have had underlying coronary artery disease and their chest discomfort may be attributed to subendocardial ischaemia unmasked by the ongoing

Table 1. Differences in demographics and clinical profile of patients with or without chest pain

Parameter	Overall (N=554)	Pneumonia			Chest pain		
		Pneumonia (n=57)	No pneumonia (n=497)	*P* value	Chest pain (n=28)	No chest pain (n=526)	*P* value
Age, years	37 (±12)	49 (±13)	36 (±11)	<0.001	37 (±9)	37 (±12)	0.977
Sex (men), no. (%)	477 (86.9)	41 (71.0)	437 (88.6)	<0.001	21 (75.0)	457 (87.5)	0.055
Medical comorbidities							
Hypertension, no. (%)	53 (12.3)	15 (32.6)	38 (9.8)	<0.001	4 (19.0)	49 (11.9)	0.332
Hyperlipidaemia, no. (%)	34 (8.1)	15 (33.3)	19 (5.0)	<0.001	2 (10.0)	32 (8.0)	0.744
Diabetes mellitus, no. (%)	21 (5.1)	7 (16.3)	14 (3.8)	<0.001	2 (10.0)	19 (4.8)	0.303
Ischaemic heart disease, no. (%)	5 (1.2)	2 (4.8)	3 (0.8)	0.084	1 (5.0)	4 (1.0)	0.114
No past medical history, no. (%)	367 (90.4)	24 (60.0)	343 (93.7)	<0.001	16 (80.0)	351 (90.9)	0.106
Symptoms							
Chest pain, no. (%)	28 (5.1)	4 (7.0)	24 (4.8)	0.517	–	–	–
Shortness of breath, no. (%)	16 (3.9)	4 (9.5)	12 (3.2)	0.068	3 (14.3)	13 (3.3)	0.041
Palpitations, no. (%)	2 (0.5)	0 (0)	2 (0.5)	0.636	1 (5.0)	1 (0.3)	0.096
Cough, no. (%)	318 (63.5)	41 (75.9)	277 (62.0)	0.051	17 (73.9)	301 (63.0)	0.287
Fever, no. (%)	275 (49.6)	34 (59.6)	241 (48.5)	0.111	15 (53.6)	260 (49.4)	0.669
Asymptomatic, no. (%)	66 (11.9)	4 (7.0)	62 (12.5)	0.228	0 (0)	66 (11.9)	0.567
Laboratory investigations							
Lymphocyte count, $\times 10^3/mm^3$	1.9 (±2.0)	1.5 (±1.1)	1.9 (±2.1)	0.100	1.6 (±0.6)	1.9 (±2.1)	0.387
Creatinine, µmol/L	79 (±30)	79 (±30)	88 (±78)	<0.001	75 (±13)	80 (±31)	0.435
AST, units/L	38 (±48)	64 (±141)	35 (±23)	<0.001	36 (±30)	38 (±49)	0.837
ALT, units/L	46 (±44)	56 (±89)	35 (±23)	0.106	50 (±74)	45 (±42)	0.652
LDH, units/L	436 (±423)	644 (±77)	414 (±360)	<0.001	381 (±110)	439 (±434)	0.492
C-reactive protein, mg/L	14 (±27)	40 (±43)	11 (±23)	<0.001	8 (±6)	14 (±27)	0.281
Ferritin, ng/mL	179 (±216)	353 (±385)	164 (±187)	<0.001	153 (±207)	180 (±216)	0.531
Elevated troponin-I (defined as trop-I>17.5ng/L), no. (%)	5 (0.9)	3 (5.3)	2 (0.4)	0.069	1 (3.6)	4 (0.8)	0.979

Table 1. Differences in demographics and clinical profile of patients with or without chest pain (Cont'd)

Parameter	Overall (N=554)	Pneumonia			Chest pain		
		Pneumonia (n=57)	No pneumonia (n=497)	*P* value	Chest pain (n=28)	No chest pain (n=526)	*P* value
Electrocardiography							
Ventricular rate, per min	79 (±16)	85 (±14)	78 (±16)	0.003	73 (±15)	79 (±16)	0.089
PR interval, ms	156 (±33)	155 (±25)	156 (±27)	0.958	145 (±27)	156 (±95)	0.557
QRS duration, ms	89 (±12)	93 (±20)	88 (±11)	0.034	93 (±18)	89 (±12)	0.094
QTc interval, ms	420 (±24)	438 (±29)	418 (±23)	<0.001	418 (±23)	419 (±25)	0.762
P axis	51 (±33)	48 (±16)	51 (±33)	0.539	47 (±20)	41 (±33)	0.499
R axis	44 (±32)	32 (±35)	45 (±31)	0.005	33 (±27)	45 (±32)	0.069
T axis	37 (±26)	43 (±51)	36 (±22)	0.088	31 (±27)	37 (±26)	0.262
Left ventricular hypertrophy, no. (%)	27 (4.9)	8 (14.0)	19 (3.8)	<0.001	2 (7.4)	25 (5.1)	0.081
T wave inversions, no. (%)	32 (5.7)	8 (14.0)	24 (4.8)	<0.001	9 (32.1)	23 (4.4)	<0.001
Ectopic beats (premature atrial contractions or premature ventricular contractions), no. (%)	7 (1.3)	0 (0)	7 (1.4)	0.836	2 (7.1)	5 (0.9)	0.008
Rhythm				0.033			0.207
Normal sinus rhythm, no. (%)	391 (75.0)	39 (70.9)	352 (75.5)	–	18 (64.3)	373 (75.7)	–
Sinus bradycardia, no. (%)	77 (14.8)	9 (16.4)	68 (14.6)	–	8 (28.6)	69 (14.0)	–
Sinus tachycardia, no. (%)	52 (10.0)	6 (10.9)	46 (9.9)	–	2 (7.1)	50 (10.1)	–
Atrial fibrillation, no. (%)	1 (0.2)	1 (1.8)	0 (0)	–	0 (0)	1 (0.2)	–
Clinical progress and outcomes							
Pneumonia, no. (%)	57 (10.3)	–	–	–	4 (14.3)	53 (10.1)	0.475
Requiring oxygen, no. (%)	16 (2.9)	8 (14.0)	8 (1.6)	<0.001	1 (3.6)	15 (2.9)	0.825
Persistent fever >72h, no. (%)	40 (7.3)	16 (29.1)	24 (4.8)	<0.001	0 (0)	40 (7.7)	0.128
Acute kidney injury, no. (%)	45 (8.1)	7 (12.3)	38 (7.6)	0.208	1 (3.6)	44 (8.4)	0.366
Required intensive care, no. (%)	19 (3.4)	13 (23.2)	6 (1.2)	<0.001	1 (3.6)	18 (3.4)	0.971
Required mechanical ventilation, no. (%)	16 (2.9)	11 (19.3)	5 (1.0)	<0.001	1 (3.6)	15 (2.9)	0.825
Myocarditis/Myocardial injury, no. (%)	3 (0.7)	3 (7.3)	0 (0)	<0.001	1 (5.0)	2 (0.5)	0.022
Death, no. (%)	2 (0.5)	2 (3.5)	0 (0)	<0.001	0 (0)	2 (0.5)	0.748

COVID-19 illness. Acute coronary syndromes may occur in COVID-19 but we did not observe any such cases.[7]

Prolonged QTc was seen in 88 (15.9%) patients. One patient had QTc>500ms. Prolonged QTc is of concern in COVID-19, given that directed therapy such as hydroxychloroquine, azithromycin and lopinavir/ritonavir may cause further QT prolongation.[8,9] Our data suggest that the QTc was prolonged by both lopinavir/ritonavir and remdesevir, with significant prolongation of the QTc post-drug administration. No malignant arrhythmia was observed with such therapies.

A widened QRS complex was seen in a minority of patients, in the form of RBBB (6 cases, 1.1%) or IVCD (8 cases, 1.4%). This was especially prominent in cases of severe disease such as those who developed pneumonia and those requiring intensive care unit and mechanical ventilation. Such a phenomenon could represent early right ventricular dysfunction, which was not unexpected given that respiratory compromise from COVID-19 especially in severe disease can drive increased afterload on the right ventricle and cause right heart dysfunction, which may be associated with higher mortality.[10]

We acknowledge that this study was retrospectively conducted, which meant we could only show association but not causation. This was a single-centre study, which may limit generalisability. In addition, given resource constraints during the response to the pandemic and the need to maintain full isolation of infected patients, very few of the patients managed to undergo further cardiac investigations. Correlation with cardiac imaging, such as transthoracic echocardiography or cardiac magnetic resonance imaging, would be useful to elucidate the significance of electrocardiographic changes and myocardial injury.

While cardiac complications are rare in young patients with minimal comorbidities, physicians should remain vigilant in watching out for warning signs and symptoms when managing these relatively well and healthy cases of COVID-19.

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Tony Yi-Wei Li *[1]*MRCP*, Jinghao Nicholas Ngiam *[1]*MRCP*, Nicholas WS Chew [2]*MRCP*, Sai Meng Tham [3]*MRCP*, Zhen Yu Lim [1]*MBBS*, Shuyun Cen [2]*MBBS*, Shir Lynn Lim [2,6]*MRCP*, Robin Cherian [2]*MRCP*, Raymond CC Wong [2,6]*FACC*, Ping Chai [2,6]*FAMS*, Tiong-Cheng Yeo [2,6]*FACC*, Paul Anantharajah Tambyah [3,6]*MD*, Amelia Santosa [4]*MRCP*, Gail Brenda Cross [3]*FRACP*, Ching-Hui Sia [2,6]*FAMS*

[1] Department of Medicine, National University Health System, Singapore
[2] Department of Cardiology, National University Heart Centre Singapore, Singapore
[3] Department of Infectious Diseases, National University Health System, Singapore
[4] Department of Rheumatology, National University Health System, Singapore
[5] Department of Haematology, National Cancer Institute Singapore, Singapore
[6] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Correspondence: Dr Ching-Hui Sia, Department of Cardiology, National University Heart Centre Singapore, 1E Kent Ridge Rd, NUHS Tower Block, Level 9, Singapore 119228.
Email: ching_hui_sia@nuhs.edu.sg
* Joint first authors