CARDIOVASCULAR MANIFESTATIONS IN COVID-19: Analysis of a Case Series of Hospital Admissions with Laboratory Confirmed SARS-CoV-2 PCR tests

Abstract
Novel COVID-19 pandemic presented primarily as a severe acute respiratory distress syndrome however, in addition to respiratory features there were many with cardiovascular presentations, not ‘typical’ of COVID-19 that caused confusion in diagnosis and management in frontline units. A case-series was undertaken in a large London Hospital to describe cardiovascular manifestations and outcomes (discharge vs death) of all patients with a laboratory confirmed SARS-CoV-2 infection, admitted from March-May 2020.

Results
In this cohort (n=855) there were 295 deaths (standardised mortality 345 per thousand admissions). Patients who had died were older; age 72.2 (SD 16.3) vs 64.8 (18.7) years, p<0.001, had similar length of stay - 12.3 (SD 9.7) vs 11.9 (SD 11.7) days. Almost 50% had pre-existing hypertension, ischaemic heart disease or atrial fibrillation, 45% had radiographic changes. Ventilatory support was required in 20% of the group who were discharged versus 44% in the those who died. Patients who were male, older, with palpitations, or pulmonary infiltrates and raised inflammatory markers were more likely to die. Following recovery, over 50% had abnormal findings on echocardiography. Therefore follow up should include a repeat echocardiogram and cardio-pulmonary assessment to explore long term sequelae.

Keywords
COVID-19; Cardiovascular manifestations;

Background
SARS-Cov-2 virus was genetically defined and identified as the cause of the COVID-19 pandemic by World Health Organisation in December 2019 (1). Within the first six months of its arrival in the human sphere, it has been responsible for nearly half-a-million deaths world-wide. Learning from the experience in China, South Korea and countries in Europe, United Kingdom developed its own preparations (2). Early descriptions of disease morphology from the data emerging from China, suggested a severe acute respiratory distress syndrome (SARS) causing profound hypoxaemia, the need for high volumes of oxygen, ventilatory support and in some cases, extra-corporeal membrane oxygenation (3). London was in the epicentre of the COVID-19 in the UK and the national health service (NHS) responded by scaling up of intensive care capacity (4). The first experience of COVID-19 in a London acute medical unit, was similar to that described in other countries with majority of patients presenting with profound hypoxaemia. However, soon we were recognising a proportion of patients with extra-pulmonary manifestations. (5)

Predominantly patients were presenting with chest pain, palpitations and a myriad of cardiovascular features, not typical of ischaemic heart disease. Early data from China suggested that acute viral myocarditis, arrhythmia and
myocardial dysfunction were likely related to a combination of factors including direct effect of the SARS-CoV-2 infection entering cells through the angiotensin converting enzyme inhibitor type 2 (ACE-2) receptors, the cytokine response and hypoxaemic myocardial injury (6). There was recognition of enhanced thromboembolic phenomena and the increased incidence of venous thromboembolism. (7) It was clear from data that pre-existing cardiovascular disease posed increased risk. However, the incidence of cardiovascular presentations and the likely extent or duration of post-COVID cardiovascular sequelae was unclear.

**Aims**

To explore the cardiovascular manifestations of SARS-CoV-2 infection in a sequential case series of patients presenting to a large teaching hospital within the epicentre in the UK, over 3 months, during the surge of COVID-19 pandemic.

**Design & Methods**

The COVID-19 case series was registered as an institutional audit and conducted with coding data from all laboratory confirmed real-time polymerase chain reaction (RT-PCR) results for naso-pharyngeal carriage of SARS-CoV-2 between 1 March to 30 May 2020. All results pertaining to members of staff were excluded. Data was collected on demographics, length of stay, clinical presentations, history of pre-existing cardiovascular disease, deaths, electrocardiography, chest radiology, echocardiography and laboratory investigations.

**Statistics**

This is an analysis of results of a cohort of patients whose data was reviewed, de-identified and analysed using parametric (Student’s t test) and non-parametric tests (Man Whitney U test). Binary logistic regression analysis was used to investigate trends for predicting the primary outcome – death or discharge. Statistical analysis was carried out using SPSS v26 (IBM Inc, USA). Results are presented with mean and standard deviation (SD). Statistical significance and confidence intervals are based on a two-tailed significance at 95%.

**Results**

**Demographics**

One thousand nine hundred and sixty five episodes coded as laboratory confirmed SARS-CoV-2 in the hospital from 1 March to 30 May 2020. Results for 63 members of staff were excluded. The remaining 1902 episodes included 905 men and 997 women. Men were older [mean 59.8 (SD 19.1) years; women 54.7 (SD 22) years; p<0.001], with a longer length of stay [mean 7.3 (SD 10.6); women 5.3 (SD 9.5) days; p<0.001]. In this cohort, all patients who were admitted to hospital were selected. One hundred sixty four patients had >1 admission during this period, out of 1019 (558 men and 461 women) so net number of unique patients was 855. The age distribution of patients admitted to hospital with COVID-19 is demonstrated in Figure 1. Figure 2 and 3 demonstrates the relationship between of age and length of stay for all patients (Fig2) and classified by gender (Fig3).

![Figure 1: Histogram showing distribution of age at the admission by gender (n=1019)](image-url)
Figure 2: Scatterplot showing the correlation between length of stay and age

Figure 3: Histogram depicting the distribution of length of stay by gender

Figure 4: Histogram demonstrating proportion of deaths (1) and discharges (0) in different age groups (1 = 16-34, 2 = 35-54, 3 = 55-74, 4 = >75 years)
In this cohort (n=855) there were 295 deaths (standardised crude mortality rate was 345 deaths per thousand). Patients who had died were older; age 72.2 (SD 16.3) vs 64.8 (18.7) years, p<0.001. The mean duration of hospital stay was similar; 12.3 (SD 9.7) vs 11.9 (SD 11.7) days, p = not significant. Figure 4 shows the rising proportionate mortality by increasing age group.

**Cardiovascular Cohort**

There were 498 / 855 patients, where complete sequential cardiovascular data sets were available for analysis, including 148 (29.6%) patients who had died. At the time of admission, 16% patients presented with ischaemic changes on their ECG and 20.8% with an arrhythmia (atrial flutter/fibrillation, bradycardia or heart block). Overall there were 69% patients with evidence of pulmonary infiltrates in the lungs, recognised as being typical of COVID-19. The subsequent analysis compares the group of patients who were discharged (Group A) with the group who died (Group B). The data in table 1, shows the comparison of demographic and clinical presentation in the cohort, based on their primary outcome. The patients in Group B, were older and a higher proportion presenting with palpitations, pulmonary infiltrates on imaging, were more likely to be needing intensive care support and have abnormal echocardiographic findings post-COVID-19. Post-COVID echocardiography showed a range of features including regional wall motion abnormalities, systolic or diastolic dysfunction, ventricular dilatation and raised pulmonary arterial pressure.
Table 1: Comparison of variables between patients who were discharged (Group A) with patients who died (Group B)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort</th>
<th>Group A (discharged)</th>
<th>Group B (died)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (Std deviation)</td>
<td></td>
<td>67.5 (17.5)</td>
<td>65.5 (17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean length of stay (Std deviation)</td>
<td></td>
<td>12.1 (11.1)</td>
<td>11.9 (11.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Gender (Percentage; men)</td>
<td></td>
<td>54.1</td>
<td>52.2</td>
<td>ns</td>
</tr>
<tr>
<td>Pre-existing cardiovascular comorbidity (percentage)</td>
<td></td>
<td>58.7</td>
<td>56.6</td>
<td>ns</td>
</tr>
<tr>
<td>Chest pain on presentation (percentage)</td>
<td></td>
<td>11.2</td>
<td>12.4</td>
<td>ns</td>
</tr>
<tr>
<td>Palpitations on presentation (percentage)</td>
<td></td>
<td>17.6</td>
<td>13.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radiological findings of COVID-19 (percentage)</td>
<td></td>
<td>69.1</td>
<td>63.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECG showing arrhythmia (percentage)</td>
<td></td>
<td>20.8</td>
<td>19.0</td>
<td>ns</td>
</tr>
<tr>
<td>ECG showing ischaemic changes (percentage)</td>
<td></td>
<td>16.0</td>
<td>16.8</td>
<td>ns</td>
</tr>
<tr>
<td>Admitted to intensive care unit (percentage)</td>
<td></td>
<td>28.7</td>
<td>20.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal echocardiographic findings</td>
<td></td>
<td>53.3</td>
<td>49.4</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 2: Comparing laboratory results between Group A (discharged) and Group B (Died)

<table>
<thead>
<tr>
<th>Group Statistics</th>
<th>Cohort</th>
<th>Group A (discharged)</th>
<th>Group B (died)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin highest level</td>
<td>228.6 (49.5)</td>
<td>136.3 (29.1)</td>
<td>426.4 (141.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>D-dimer (on admission)</td>
<td>1764.8 (140.6)</td>
<td>1386.6 (151.5)</td>
<td>2432.3 (266.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP highest level</td>
<td>228.3 (26.9)</td>
<td>137.9 (6.7)</td>
<td>435.9 (83.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nt-pro BNP level</td>
<td>5622.2 (836.4)</td>
<td>4452.7 (839.2)</td>
<td>8445.0 (1978.2)</td>
<td>0.031</td>
</tr>
<tr>
<td>Lymphocyte lowest level</td>
<td>0.83 (0.07)</td>
<td>0.83 (0.03)</td>
<td>0.85 (0.23)</td>
<td>ns</td>
</tr>
</tbody>
</table>

P values calculated by Student’s t test; SEM standard error of mean.

Figure 5: Box plots displaying the laboratory bio-markers of inflammation, cardiac injury and dysfunction for patients based on Group A = 0/B = 1.
In table 2, comparative data shows that patients in Group B had significantly higher values for markers of inflammation, myocardial injury (Troponin) and cardiac dysfunction (nt-pro BNP). Figure 5 shows boxplots depicting the biomarkers compared between Groups A & B. Binary logistic regression analysis of the data demonstrated that male sex (p=0.02), infiltrates in chest radiograph (p<0.001), a high C-reactive protein (p=0.04) were associated with an independent increased risk of death while a higher lymphocyte count (p=0.015) and ICU admission (p=0.009) were protective.

Discussion
Since its first recognition and characterisation in Wuhan, China in December 2019, the COVID-19 pandemic caused by SARS-CoV-2 has produced a significant and unprecedented upturn in the scientific and investigative collaboration across the world. When the surge travelled across the world reaching Europe and UK, there was a plethora of data emerging from various epicentres. Scientists, health service leaders and almost all governments in countries across the world that were following the temporal progression of the spread, were keen to learn the necessary lessons and prepare. While the initial limelight was on ARDS and the need for ventilatory support at a massive scale, there was early recognition that a substantial proportion of patients may not have the classical fever, cough and hypoxia; that many may have mild and therefore unrecognisable disease posing a significant risk of spreading infection. It was important therefore to describe and learn of the extra-pulmonary manifestations (3,8), so health care systems could remain alert and aware.

One of these early manifestations was in cardiovascular or cardio-pulmonary involvement. We were aware of patients in March 2020, presenting with atypical chest pain, palpitations and laboratory evidence of acute myocardial injury (6). What was unclear at this time, was how this may impact on the early outcomes from COVID-19 and what sequelae might there be to patients who survived. Hence, it was important to explore the extent of cardiovascular involvement in patients presenting to hospital with laboratory proven SARS-CoV-2 infection, describe the extent of this involvement and how this may relate to their outcome. It was also recognised early, that patients with underlying cardiovascular disease appeared to be at higher risk of severe disease and mortality. (9)

From a demographic perspective, we did not find a difference in patients requiring admission based on gender, there was a preponderance of patients above the age of 50 years and when adjusted for age, men were more likely to feature in the group who succumbed to their illness. In this respect, our data matched the results from other parts of the world. The average length of stay was as expected with no real difference between those who survived and those who did not. Most data suggests between 10-14 days for the ‘cytokine storm’ and commencement of multi-organ failure. Just under 70% of patients had infiltrates in their chest radiograph and this feature was more common in patients who succumbed.

Our data showed that more than half of all patients requiring admission to hospital due to COVID-19, had underlying cardiovascular co-morbidity in the form of hypertension, ischaemic heart disease or atrial fibrillation. This was not surprising given the age group of a large proportion of patients, the underlying population prevalence and the data from other countries showing increased risk of infection or poor outcomes. However, our data did not indicate that pre-existing cardiovascular disease predicted mortality in this cohort. Our data did show that patients presenting with palpitations, and demonstrating evidence of acute myocardial injury (troponin) did not fare well and were over-represented in the group of patients who died. There was also significant correlation with non-specific biomarkers of inflammation (C-reactive protein and D-Dimer). The nt-pro-BNP results as a marker of acute cardiopulmonary dysfunction/ stress were significantly correlated with a poor outcome in this cohort. It is also not surprising that patients with more severe disease, requiring intensive care support were more likely to feature in the group who died.

What is interesting is the data suggesting that around half of patients had evidence of myocardial dysfunction in their post-COVID-19 echocardiograms. Predominantly this was in the form of diastolic or systolic dysfunction, chamber dilatation and regional wall motion abnormalities. It is likely that these patients may experience a degree of medium to longer term sequelae in the form of myocardial dysfunction and therefore will need a follow up cardiology imaging and review.

There are limitations to our case series. The identification of patients was based on those with laboratory positive RT-PCR tests undertaken during the target months. We then excluded all staff and patients who did not require hospital admission. This would mean that we were unable to comment on or compare data with patients with mild symptoms, expected to be younger, with lesser co-morbidities and their sequelae. We were also not able to include patients, albeit a small proportion, who had clinical features of COVID-19, but had negative laboratory swab test. As our audit was focussed on cardiac manifestations, we were also not able to collect or review the presence of other symptoms such as anosmia, fever, gastro-intestinal or neuro-cognitive features. Exploration of these would allow for a more comprehensive description of this cohort of patients. Our data analysis was dependent on access to
hospital electronic patient records and if the patients following discharge, deteriorated, required admission to another neighbouring hospital, we would not be aware of this or any subsequent outcomes.

Conclusions
Our case series was designed to explore the extent of cardiovascular involvement for SARS-CoV-2 infection, describe the morphology and outcomes as a result. After, pulmonary disease (ARDS), cardiac injury is likely to contribute to severity of pathological involvement and have a significant bearing on outcome. We found that acute myocardial injury is common, related to presentation with palpitations and resulted in a high proportion of cardiac dysfunction in survivors. Subsequent focus should be on range and extent of medium to long term sequelae in this cohort of survivors.

Authors contributions
IC & NK designed the study, analysed the data and wrote the manuscript. All other authors contributed to the data collection, review and editing of the manuscript.

References