Evaluating the role of transthoracic echocardiography in hospitalised patients with COVID-19 infection

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# Abstract

**Objective**

To identify the most common transthoracic echocardiogram (TTE) parameters in patients hospitalised with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) and their association with myocardial injury and outcomes.

**Methods**

A retrospective, single-centre, observational, exploratory cohort study was performed at the height of the COVID-19 pandemic. All SARS-CoV-2 polymerase chain reaction (PCR) positive patients who underwent a TTE during their inpatient admission between 1st March 2020 and 31st October 2020 were analysed. The most frequent cardiovascular risk factor profile and echocardiographic features were investigated.

 **Results**A total of 87 patients met the eligibility criteria. A salient 41.4% (n=36) of our cohort succumbed to this devastating virus. More than half of our hospital population (58.6%) were admitted to the intensive care unit (ITU) and this was significantly associated with inpatient mortality (OR 7.14, CI 2.53 – 20.19, p < 0.001). Hypertension was the most common cardiovascular risk factor (51.7%) with no additional prominence in non survivors (OR 2.33, CI 0.97 – 5.61, p = 0.059). Remarkably, 90.8% of our cohort demonstrated a preserved left ventricular ejection fraction although 69.1% had elevated troponin levels. Only 1 patient (1.1%) were given a diagnostic label of myocarditis. A raised pulmonary artery systolic pressure (36.8%) and right ventricular (RV) dysfunction (26.4%) were the most common echocardiographic features. In particular, the presence of RV dysfunction was significantly related to adverse outcomes (OR 2.97, CI 1.11 – 7.94, p < 0.03). **Conclusions**In this cohort of extremely unwell patients hospitalised with COVID pneumonitis, the presence of RV dysfunction or admission to ITU was significantly associated with inpatient case fatality ratio. Moreover, COVID-19 induced myocarditis remains extremely rare.

**Key Words** – COVID-19; SARS-CoV-2; Echocardiography; Cardiac imaging; Right Ventricle; Hypertension

# Key Messages

**What is already known about this subject?**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pandemic presents one of the greatest medical challenges of our generation. Whilst commonly causing a viral pneumonitis, it has significant and profound effects on the cardiovascular system. Myocardial damage in this cohort of patients is well recognised and is highlighted by the notable rise in troponin. However, the mechanism of myocardial injury remains convoluted.

**What does this study add?**

In this retrospective, observational survey, 69.1% of patients had elevated troponin levels but over 90% of patients had a preserved left ventricular function. Both elevated pulmonary artery systolic pressure (PASP) and right ventricular (RV) dysfunction were the most common echocardiographic features with RV dysfunction significantly associated with inpatient mortality. There was no significant relationship between in-patient death and prominent cardiovascular risk factors.

**How might this impact on clinical practice?**

Characterising the presence of RV dysfunction is a valuable tool in the risk stratification of patients hospitalised with COVID-19. Additionally, COVID-19 induced myocarditis is rare and troponin elevation is likely to represent the phenotype of a severe respiratory illness.

**Abbreviations:**

ACE-2 - Angiotensin-Converting Enzyme 2
ACS - Acute Coronary Syndrome
ARDS - Acute Respiratory Distress Syndrome
ASE - American Society Of Echocardiography
AF - Atrial Fibrillation
BMI - Body Mass Index
BSE - British Society of Echocardiography
CAD - Coronary Artery Disease
CK - Creatine Kinase
CKD - Chronic Kidney Disease
CMRi - Cardiac Magnetic Resonance Imaging
COPD - Chronic Obstructive Pulmonary Disease
COVID-19 - Coronavirus
CV - Cardiovascular
EACVI - European Association of Cardiovascular Imaging
EF - Ejection Fraction
HCRW - Health and Care Research Wales HRA - Health Research Authority
ITU - Intensive Care Unit
IQR – Interquartile Range
LA - Left Atrium
LDH - Lactate Dehydrogenase
LGE - Late Gadolinium Enhancement
LVEF - Left Ventricular Ejection Fraction
LVIDd - Left Ventricular End Diastolic Dimensions
LVNC - Left ventricular non-compaction cardiomyopathy
MERS-CoV - Middle East Respiratory Syndrome Coronavirus
Non-ST Elevation Myocardial Infarction – NSTEMi
PASP - Pulmonary Artery Systolic Pressure
PCR – Polymerase Chain Reaction
PE - Pulmonary Embolus
HFrEF - Heart Failure with Reduced Ejection Fraction
RV - Right Ventricle
SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2
SD – Standard Deviation
SVT – Supra-Ventricular Tachycardia
TAPSE - Tricuspid annular plane systolic excursion
TTE - Transthoracic Echocardiogram
WCC - White Cell Count

# Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), otherwise known as the coronavirus (COVID-19) pandemic presents one of the greatest medical challenges of our generation. Whilst commonly causing a viral pneumonitis, COVID-19 can trigger widespread and systematic insults largely precipitated through a cytokine storm 1 . This can have profound and disastrous effects on the cardiovascular system.

Both the lungs and the heart express the angiotensin-converting enzyme 2 (ACE-2) protein which has been acknowledged as the port of entry for SARS-CoV-2 1 . With respect to the myocardium, cardiac myocytes and fibroblasts both express the ACE-2 receptor abundantly and studies have demonstrated that ACE-2 levels correlate with the extent of pathological left ventricular remodelling 1 2 3 .

Myocardial injury in COVID-19 is well recognised and is characterised by a significant elevation in troponin levels, especially in individuals with severe infection which necessitated hospitalisation 4 5. However, the exact mechanisms of this elevation remain uncertain. Yet, the value of this biochemical marker is critical in prognosticating patients infected with COVID-19 given the correlation between elevated levels and adverse outcomes 5 6 7. Although troponin is classically used to identify a type 1 myocardial infarction, multiple non-ischemic processes such as hypoxemia, venous thromboembolism, systemic inflammatory response, tachyarrhythmias and myocarditis contribute to this biochemical phenomenon in COVID-19 4 5 6 7.

Transthoracic echocardiogram (TTE) has been widely utilised in hospitalised COVID-19 patients to elucidate the aetiology of myocardial damage. Given its extensive availability, cost-effectiveness and non-invasive approach it is universally recommended as the first line imaging modality to assess the structure and the function of the heart 8 9. However, due to the transmissibility and fatality rate of the SARS-CoV-2, leading societies only recommend the use of echocardiography if it is deemed to alter the management trajectory 10. As data regarding echocardiographic findings in COVID-19 remains sparse and inconclusive, we aim to add to the growing body of literature to identify the most frequent TTE parameters in patients hospitalised with COVID-19 and its association with myocardial injury and outcomes.

# Methods

## Study Design

A retrospective review of all patients admitted with a COVID-19 polymerase chain reaction (PCR) positive swab who underwent a TTE between 1st March 2020 and 31st October 2020 at our institution was performed. All patients were greater than 18 years of age and only the index echocardiogram was included in the analyses. Patients with a previous echo indicative of heart failure with reduced ejection fraction (HFrEF) were excluded. The study was conducted without any patient or public involvement.

## Data Collection

Pertinent demographic variables such as age, gender, ethnicity, height (cm) and weight (kg) were collected using the electronic healthcare records (Cerner, Missouri, USA). The presence of other diagnostic labels such as hypertension, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), coronary artery disease (CAD), stroke and atrial fibrillation (AF) were also obtained. Peak high sensitivity troponin I (hs-cTnI) (ng/L) levels and the diagnosis of a new pulmonary embolus (PE) made during the inpatient admission was also noted. At our institution hs-cTnI was considered elevated if it was > 16 ng/L in females or > 30 ng/L in males. Other variables such as admission to intensive care unit (ITU), presence of a cardiovascular diagnosis on discharge and inpatient death were retrieved.

## Echocardiogram

Scans were performed by British Society of Echocardiography (BSE) accredited sonographers in accordance with the BSE COVID-19 protocol 11. A level 1 BSE scan was performed in all patients with no ECG gating. Images were acquired by a GE Vivid Q ultrasound machine (GE Healthcare, Horten, Norway). At our institution, the GE EchoPAC PC V204 software was utilised to obtain measurements in accordance with the joint American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines 8 9.

Echocardiographic variables such as left ventricular end diastolic dimension (LVIDd) (cm); left ventricular ejection fraction (EF) (%); left atrial size (cm); right atrial area (cm2); right ventricle (RV) size (cm); tricuspid annular plane systolic excursion (TAPSE) (cm) and pulmonary artery systolic pressure (PASP) (mmHg) were collected. Left ventricular impairment was defined as a left ventricular ejection fraction (LVEF) ≤ 50%. LVEF was calculated by the Simpson’s biplane method:

((End diastolic volume – End systolic volume)/End diastolic volume) x 100

In addition, the presence of left ventricular dilatation was determined by a LVIDd > 5.2 cm in females and a LVIDd > 5.8 cm in males. Further, RV dysfunction was defined as either a dilated RV, reduced TAPSE or an impaired right ventricle radial function either objectively or visually at the discretion of the echocardiographer. A dilated left atrium (LA) was identified either as an antero-posterior dimension of ≥ 4cm; an indexed volume of ≥ 34 ml/m2 or a volume of > 54ml when BSA was not available for indexing. Right atrial dilatation was identified as an area ≥ 18cm2. A TAPSE < 1.7cm was defined as abnormal and a PASP ≥ 35mmHg was suggestive of raised pulmonary artery pressures.

## Statistical Analyses

All the variables have been graphically inspected and summarize according to their statistical nature, i.e. means, standard deviation, medians, inter-quartile values and ranges for continuous variables and proportions for categorical data with marginal percentages by hospital outcome. Logarithmic transform was considered where appropriate.

Exact logistic regression on a binary response defined by the hospital outcome to assess its associations with the available variables in the data measured by odds ratios (OR). An OR greater than one indicates a harmful effect whilst an OR smaller than 1 indicates a protective effect. The level of significance was deemed as 0.05 and the uncertainties were expressed as 95% CIs. The relatively small dataset prevented a reliable multivariable model and the exploratory aspect of the analyses did not require adjustments for the alpha level of significance.

All analyses have been conducted in STATA (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC)

## Ethics

Ethical approval was granted by the Health Research Authority (HRA) and Health and Care Research Wales (HCRW). The integrated research application system identification number is 286146.

# Results

During this 8-month period, a total of 90 patients with COVID-19 pneumonia underwent an echocardiogram. Out of these, 87 met the eligibility criteria (Figure 1). Baseline characteristics including demographics, co-morbidities, biomarkers and relevant echocardiographic findings are illustrated in Table 1. Majority of the referrals for echocardiography were primarily due to elevated troponin levels (n=53, 60.9%), followed by assessment of baseline left ventricular function (n=8, 9.2%). An abnormal ECG in isolation accounted for only 1 referral, however, an abnormal ECG together with a raised troponin level resulted in 7 (8%) echocardiograms being performed. Furthermore, a clinical suspicion of acute coronary syndrome (ACS) alongside an abnormal troponin led to 5 (5.7%) echocardiograms being completed.

## Patient characteristics

A salient 41.4% (n=36) of the study population succumbed to this devastating virus. The mean age of the cohort was 62 + 14.8 years of age and there was no significant difference observed between those who died and those who survived (64 + 13.7 vs 61.5 + 15.6, OR 1.01, CI 0.98 – 1.04, p = 0.43). Males comprised 55.2% (n=48) of the cohort. Our population demographics represents a high proportion of patients of black and minority ethnic origin (BAME) (60.9%, n=53). Notably, they were not at a higher risk of mortality from COVID-19 when compared to Caucasians (OR 0.97, CI 0.37 – 2.50, P = 0.95).

An overwhelming majority of the cohort were overweight with 65.5% (n=57) exhibiting a body mass index (BMI) of > 25 kg/m2. The mean BMI of the cohort was elevated at 29.8 + 6.9 kg/m2 but there was no statistical significance demonstrated between obesity (BMI > 30 kg/m2) and inpatient mortality (OR 1.14, CI 0.43-3.0, p < 0.79). Other notable cardiovascular (CV) risk factors included hypertension (51.7%) and diabetes (33.3%) (Figure 2). There was no significant link observed between the presence of cardiovascular risk factors and inpatient death, although a diagnostic label of hypertension was close to achieving statistical significance (OR 2.33, CI 0.97 – 5.61, p = 0.059). More than half of the cohort (58.6%) was admitted to ITU and out of the 36 patients who died, 30 (83.3%) passed away in the ITU setting. Intuitively, admission to ITU was associated with an increased risk in mortality (OR 7.14, CI 2.53 – 20.19, p < 0.001).

## Transthoracic Echocardiogram

Overall, 90.8% (n=79) of the cohort had a preserved left ventricular ejection fraction (LVEF). The mean LVEF of our population was 60.7 + 10 % and there were no significant differences between survivors and non-survivors (59.8% vs 62.1%, p = 0.30). Markedly, 91.7% (n=33) of the non-survivors cohort had a preserved LVEF. A raised PASP (36.8%) was the most common echocardiographic feature exemplified in our cohort although this was not related to mortality (OR 1.84, CI 0.56 – 6.05, p < 0.32). Numerically, the mean PASP was considerably higher in those who died (44.5 + 14.2) when compared those who survived (38.5 + 11.1). Importantly, RV dysfunction was demonstrated in 26.4% of patients and this was associated with associated with a three-fold increase in death (OR 2.97, CI 1.11 – 7.94, p < 0.03). Both the left (22.2%, n=18) and right (21.3%, n=16) atria were dilated in less than a quarter of patients with no relation to fatality (p = 0.08 and p = 0.36 respectively). With regards to left ventricular remodelling, the mean left ventricle size was significantly higher in those who survived (4.6 + 0.5 cm vs 4.2 + 0.7 cm). Nonetheless, it is critical to recognise that the mean LV size for both subgroups was well within normal limits with only 4.9% (n=4) of the overall cohort having a dilated left ventricle.

Eighteen (20.7%) patients subsequently underwent a repeat TTE during their inpatient admission. Sixteen (88.8%) out of the 18 repeat TTE’s were performed in ITU patients. From the 13 patients with a raised PASP on the initial echocardiogram (all ITU patients), 7 (53.8%) improved their right sided pressures with 4 (30.8%) normalising their pulmonary artery pressures. However, 7 (53.8%) individuals still had persistently elevated PASP on repeat imaging. Only 1 out of the 4 patients with normalised PASP eventually expired. However, 85.7% (n=6) of the patients with persistently raised PASP’s died.

## Troponin

Troponin levels were performed in 81 (93.1%) patients. Elevated levels were observed in 69.1% (n=56) of our cohort with raised levels occurring more frequently in women (71.8%) compared to men (58.3%). The median peak troponin was numerically higher in the patients who died when rivalled to those who survived (71.2 ng/L vs 45.3ng/L, OR 1.14, 95% CI 0.88- 1.47, p < 0.32).

## Cardiovascular Outcomes

Fifteen patients (18.4%) had a concomitant cardiovascular diagnosis during their admission with 8 (9.2%) patients diagnosed with AF or a supra-ventricular tachycardia (SVT). Five patients (5.7%) were diagnosed with a Non-ST Elevation Myocardial Infarction (NSTEMI). However, it is important to note that out of these patients, only 1 underwent coronary angiography and subsequent percutaneous coronary intervention (PCI). Two patients were admitted to ITU for concomitant severe COVID pneumonitis and were too unstable to undergo coronary angiography and were treated medically. Moreover, 1 patient had a poor functional status and his frailty precluded him from undergoing coronary angiography. The remaining 1 patient was planned to undergo an outpatient computed tomography coronary angiography (CTCA). Additionally, one (1.1%) patient was given a diagnostic label of myocarditis after a coronary angiogram revealed a non-ischaemic cause of chest pain and troponin rise. Finally, one patient was newly diagnosed with left ventricular non-compaction cardiomyopathy (LVNC).

# Discussion

Our study represents an extremely sick cohort of patients with an ITU admission rate of 58.6% and an inpatient mortality rate of 41.4% at a busy East London district general hospital. Remarkably, over 90% of the cohort demonstrated a preserved LVEF. Both a raised PASP and RV dysfunction were markedly prevalent with RV dysfunction in particular exhibiting a significant link with inpatient mortality. This corroborates with data from Europe and USA 12 13 14 15. In particular, Wats et al (2021) established that poorer the RV function the higher the risk of death from COVID-19 13. Further, sequalae of RV dysfunction such as tricuspid regurgitation (TR), specifically moderate to severe TR, also displayed an increased association with adverse outcomes. Studies have also demonstrated a relationship between elevated PASP and an increased risk in mortality, however, we did not ascertain a correlation between these two variables 12 13. It is perceptive that both RV dysfunction and raised PASP are likely to represent a phenotype of the severe respiratory illness from COVID pneumonitis rather than direct, isolated RV damage from the virus. As such, our dataset demonstrated that 53.8% (n=7) of the ITU cohort with raised PASP’s who underwent serial echocardiography improved their pulmonary pressures likely as a result of the superior ventilation provided by mechanical respiratory support. This once again offers evidence for the role of respiratory pathology as the main contributor to the elevated right heart pressures and dysfunction in COVID-19. In fact, a literature review of cardiac autopsies from COVID-19 patients revealed myocarditis in only 20 out of 277 (7.2%) patients 16. Moreover, this was likely to be an overestimate given the lack of standardisation and rigour in recognising myocarditis in post-mortem studies. From a cardiovascular point of view, this is reassuring and recent Cardiac Magnetic Resonance Imaging (CMRi) analysis of 149 healthcare workers with mild COVID-19 infection demonstrated a late gadolinium enhancement (LGE) pattern consistent with myocarditis in only 4% of individuals after 6 months from the initial incubation 17. Our echocardiographic data reiterates these findings with only 1.1% of our cohort having a diagnostic label of myocarditis. Whilst COVID-19 primarily insults the lung parenchyma through direct invasion via the ACE-2 receptors, pulmonary embolism (PE) has also been widely reported as a consequence of the systemic and vascular inflammation 1 18. A combination of both viral pneumonitis and thrombosis of the pulmonary arteries are postulated to play a critical role in the development of RV dysfunction.

In a subset of patients who underwent repeat echocardiography, there was a signal towards the utility of PASP as a prognostic marker, as those with persistently raised pulmonary pressures were more likely to succumb to SARS-CoV2. In line with this, retrospective observational data from New York, USA (n=214) identified the important association between elevated pulmonary pressures and death in the hospital population (OR 5.39, CI 1.96-14.86, p < 0.001) 13. Additionally, elevated PASP was also linked to a need for vasopressor support and mechanical ventilation which is instinctive given that elevated right sided pressures are a direct result of severe COVID-19 pneumonitis +/- pulmonary embolism 13. Furthermore, a raised PASP with simultaneous reduction in TAPSE (TAPSE/PASP ratio) has also been demonstrated to be an independent marker of poor outcomes in COVID-19 Acute Respiratory Distress Syndrome (ARDS) and adds additional value to the traditionally used Berlin Criteria in prognostication 19. However, given the variability in accurately measuring PASP through echocardiography and particularly in patients on respiratory support, this will need to be studied in a prospective, rigorous and standardised manner before being used for prognostication purposes in COVID-19 patients.

Cardiac troponin was notably elevated in the majority of our study population (69.1%). However, this elevation was not characterised by an increase in mortality in contrast to contemporary data 4 5 20. When rivalled to other biomarkers, troponin has been shown to be superior for prognostication purposes. Zhou et al (2020) elucidated that in 191 hospitalised patients with COVID-19, troponin I had an odds ratio of 80.1 (CI 10.34 – 620.36, p < 0.0001) in predicting mortality, a figure significantly more prominent when compared to D-Dimer, lactate dehydrogenase (LDH), creatine kinase (CK) and white cell count (WCC). Although troponin I elevation is classically interconnected with an acute coronary syndrome (ACS), case series have shown that in those infected with COVID-19 who present with ST segment elevation on electrocardiogram, a substantial percentage have unobstructed coronary arteries 21 22. In addition, post-mortem analyses have also highlighted the infrequency of acute myocardial infarctions in the COVID-19 cohort 16. Therefore, the mechanisms of troponin leak in these patients remain multifactorial and predominantly non-ischemic. These include indirect myocardial injury secondary to severe hypoxia, sepsis, systemic inflammation, pulmonary embolism and rarely from direct myocardial injury from stress cardiomyopathy or myocarditis. Another proposed mechanism for this phenomenon can be related to the degree of RV dysfunction and our data underscores this association with 78.2% of patients with RV dysfunction expressing elevated troponin levels. Out of the seven patients with troponin values > 900 ng/L, five (71.4%) conveyed RV dysfunction on their echocardiogram.

We did not establish a significant relationship between the presence of hypertension and inpatient mortality. However, this was perishingly close to statistical significance and the overwhelming majority of current literature provide striking evidence for this connection 5 6 23 24. Further, this link was echoed during the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012 which shares analogous pathogenesis to SARS-CoV2 25 26. The co-existence of hypertension along with other cardiovascular risk factors such as diabetes, CKD and CAD predisposed patients to MERS-CoV as well as considerably increasing their risk of death. Data from Wuhan, the epicentre of SARS-CoV2, additionally demonstrated a preponderance of COVID-19 to individuals with underlying hypertension and its significant relation to mortality (OR 3.05, CI 1.57-5.92, p < 0.0010) 6. Intriguingly, a meta-analysis of 48, 317 COVID-19 infected patients exhibited that younger patients (<50 years) with hypertension had a higher fatality rate than older patients (>60 years) with the same comorbidity 23. Whereas numerous studies have also shown diabetes, obesity and underlying coronary artery disease to also be a poor prognostic sign, we were again unable to reverberate these findings 27. Overall, the reason for increased prevalence of hypertension in the COVID-19 cohort remain unclear and convoluted. A plausible explanation is that hypertension predisposes COVID-19 individuals to myocardial injury which perpetuates poorer blood pressure control and thus leading to adverse outcomes 28 29. The initial theories suggesting the role of upregulation of ACE-2 receptors in those with underlying hypertension have been widely disproved 24 28. In the non COVID-19 cohort, plasma ACE-2 levels have shown to be notably elevated as well as associated with adverse outcomes in those with AF, obstructive CAD and aortic stenosis 2 3 30. Recent COVID-19 literature have similarly demonstrated prominent levels of plasma ACE-2 in those infected with SARS-CoV-2 in addition to being a prognostic compass 30. Therefore, this novel biomarker is an exciting and definite area which requires more detailed characterisation to fully recognise its value in improving outcomes from this destructive virus.

## Limitations

Numerous limitations exist within our study. Firstly, as a retrospective, observational study there is an inherent selection bias and inability to control confounding variables. Secondly , only patients who the parent team viewed as appropriate for an echocardiogram were examined and hence there was a large cohort of hospitalised COVID-19 patients we did not capture. In addition, only patients with a positive PCR result were included and there is probably a proportion of patients with false negative PCR results who were not studied. Furthermore, our data is only applicable to the hospital population and does not apply to the large majority of patients with mild COVID-19 infection. In accordance with the BSE COVID-19 protocol, level 1 scans were performed, and thus valvular pathology was not expertly analysed. Finally, death from an alternative aetiology other than COVID-19 cannot be fully excluded but given that the hospital admissions during our study period were virtually all COVID-19 presentations, it is extremely likely that all inpatient mortality was directly attributable to SARS-CoV-2.

# Conclusions

Our single-centre, retrospective cohort study exhibits a critical contribution to the COVID-19 literature. Remarkably, in this extremely ill cohort of patients who died, over 90% of patients had a preserved LVEF. Moreover, admission to ITU or echocardiographic evidence of RV dysfunction in the hospitalised COVID-19 population signifies a trend towards poorer outcomes. Thus, indicating that the echocardiographic phenotype associated with adverse events is more consistent with a severe respiratory illness rather than direct myocardial injury from SARS-CoV-2.

# Contributorship Statement

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All Authors (AB, ZM, NE, DL, JN, RTB, ICS, JB, VV) contributed to the proposal of the research project, data analysis and interpretation as well as the writing and revision of the manuscript. Statistical analyses were performed by ICS. Further, corresponding author AB is the recognised guarantor for this piece of original research.

# Conflicts of Interest

The authors have no conflicts of interest to declare and have had no previous or exisiting relationship with industry.

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# Data availability statement

Data are available on reasonable request. All data pertinent to the study are presented in the research article.

# References

1. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: From basic mechanisms to clinical perspectives. *Nat Rev Cardiol*. 2020;17(9):543-558. Accessed Apr 29, 2021. doi: 10.1038/s41569-020-0413-9.

2. Walters TE, Kalman JM, Patel SK, Mearns M, Velkoska E, Burrell LM. Angiotensin converting enzyme 2 activity and human atrial fibrillation: Increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling. *Europace*. 2017;19(8):1280-1287. Accessed May 18, 2021. doi: 10.1093/europace/euw246.

3. Ramchand J, Patel SK, Kearney LG, et al. Plasma ACE2 activity predicts mortality in aortic stenosis and is associated with severe myocardial fibrosis. *JACC Cardiovasc Imaging*. 2020;13(3):655-664. Accessed May 18, 2021. doi: 10.1016/j.jcmg.2019.09.005.

4. Imazio M, Klingel K, Kindermann I, et al. COVID-19 pandemic and troponin: Indirect myocardial injury, myocardial inflammation or myocarditis? *Heart*. 2020;106(15):1127-1131. Accessed Apr 29, 2021. doi: 10.1136/heartjnl-2020-317186.

5. Qin J, Cheng X, Zhou F, et al. Redefining cardiac biomarkers in predicting mortality of inpatients with COVID-19. *Hypertension*. 2020;76(4):1104-1112. Accessed Apr 30, 2021. doi: 10.1161/HYPERTENSIONAHA.120.15528.

6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in wuhan, china: A retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Accessed Apr 30, 2021. doi: 10.1016/S0140-6736(20)30566-3.

7. Chapman AR, Bularga A, Mills NL. High-sensitivity cardiac troponin can be an ally in the fight against COVID-19. *Circulation*. 2020;141(22):1733-1735. Accessed Apr 30, 2021. doi: 10.1161/CIRCULATIONAHA.120.047008.

8. Harkness A, Ring L, Augustine DX, Oxborough D, Robinson S, Sharma V. Normal reference intervals for cardiac dimensions and function for use in echocardiographic practice: A guideline from the british society of echocardiography. *Echo research and practice*. 2020;7(1):G1-G18. <http://dx.doi.org/10.1530/ERP-19-0050>. doi: 10.1530/ERP-19-0050.

9. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the american society of echocardiography and the european association of, cardiovascular imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17(4):412. Accessed Apr 30, 2021. doi: 10.1093/ehjci/jew041.

10. Skulstad H, Cosyns B, Popescu BA, et al. COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel. *Eur Heart J Cardiovasc Imaging*. 2020;21(6):592-598. Accessed Jun 1, 2021. doi: 10.1093/ehjci/jeaa072.

11. D.Augustine, J.Willis, S.Robinson, et al. CV-19 BSE TTE consensus pathway . . 2020:1. <https://www.bsecho.org/Common/Uploaded%20files/Education/COVID-19/COVID-19%20TTE%20pathway.pdf>.

12. D’Andrea A, Scarafile R, Riegler L, et al. Right ventricular function and pulmonary pressures as independent predictors of survival in patients with COVID-19 Pneumonia. *JACC Cardiovasc Imaging*. 2020;13(11):2467-2468. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7314435/>. Accessed May 15, 2021. doi: 10.1016/j.jcmg.2020.06.004.

13. Wats K, Rodriguez D, Prins KW, et al. Association of right ventricular dysfunction and pulmonary hypertension with adverse 30-day outcomes in COVID-19 patients. *Pulm Circ*. 2021;11(2):20458940211007040. <https://doi.org/10.1177/20458940211007040>. Accessed May 15, 2021. doi: 10.1177/20458940211007040.

14. Mahmoud-Elsayed HM, Moody WE, Bradlow WM, et al. Echocardiographic findings in patients with COVID-19 pneumonia. *Can J Cardiol*. 2020;36(8):1203-1207. Accessed May 16, 2021. doi: 10.1016/j.cjca.2020.05.030.

15. Crook RL, Williams H, Green M, et al. Prospective multicentre cohort study of transthoracic echocardiography provision in the south west of the UK during the first wave of SARS-CoV-2 pandemic. *Open Heart*. 2021;8(1). Accessed May 16, 2021. doi: 10.1136/openhrt-2020-001409.

16. Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: Cardiovascular findings across 277 postmortem examinations. *Cardiovasc Pathol*. 2021;50:107300. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7583586/>. Accessed May 15, 2021. doi: 10.1016/j.carpath.2020.107300.

17. Joy G, Artico J, Kurdi H, et al. Prospective case-control study of cardiovascular abnormalities 6 Months Following mild COVID-19 in Healthcare workers. *JACC: Cardiovascular Imaging*. 2021. <https://www.sciencedirect.com/science/article/pii/S1936878X21003569>. Accessed May 15, 2021. doi: 10.1016/j.jcmg.2021.04.011.

18. Jevnikar M, Sanchez O, Humbert M, Parent F. Prevalence of pulmonary embolism in patients with COVID-19 at the time of hospital admission and role for pre-test probability scores and home treatment? *Eur Respir J*. 2021. Accessed May 15, 2021. doi: 10.1183/13993003.01033-2021.

19. D'Alto M, Marra AM, Severino S, et al. Right ventricular-arterial uncoupling independently predicts survival in COVID-19 ARDS. *Crit Care*. 2020;24(1):670. Accessed May 16, 2021. doi: 10.1186/s13054-020-03385-5.

20. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. *Prog Cardiovasc Dis*. 2020;63(3):390-391. Accessed May 15, 2021. doi: 10.1016/j.pcad.2020.03.001.

21. Bangalore S, Sharma A, Slotwiner A, et al. ST-segment elevation in patients with covid-19 — A case series. *New England Journal of Medicine*. 2020;382(25):2478-2480. <https://doi.org/10.1056/NEJMc2009020>. Accessed May 16, 2021. doi: 10.1056/NEJMc2009020.

22. Saririan M, Armstrong R, George JC, et al. ST-segment elevation in patients presenting with COVID-19: Case series. *European Heart Journal - Case Reports*. 2021;5(ytaa553). <https://doi.org/10.1093/ehjcr/ytaa553>. Accessed May 16, 2021. doi: 10.1093/ehjcr/ytaa553.

23. Bae S, Kim SR, Kim M, Shim WJ, Park S. Impact of cardiovascular disease and risk factors on fatal outcomes in patients with COVID-19 according to age: A systematic review and meta-analysis. *Heart*. 2021;107(5):373-380. <https://heart.bmj.com/content/107/5/373>. Accessed May 16, 2021. doi: 10.1136/heartjnl-2020-317901.

24. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–Angiotensin–Aldosterone system inhibitors and risk of covid-19. *New England Journal of Medicine*. 2020;382(25):2441-2448. <https://doi.org/10.1056/NEJMoa2008975>. Accessed May 16, 2021. doi: 10.1056/NEJMoa2008975.

25. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in wuhan, china. *The Lancet (British edition)*. 2020;395(10223):497-506. [http://dx.doi.org/10.1016/S0140-6736(20)30183-5](http://dx.doi.org/10.1016/S0140-6736%2820%2930183-5). doi: 10.1016/S0140-6736(20)30183-5.

26. Assiri A, MD, Al-Tawfiq JA, FACP, Al-Rabeeah AA, FRCS, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of middle east respiratory syndrome coronavirus disease from saudi arabia: A descriptive study. *The Lancet infectious diseases*. 2013;13(9):752-761. <https://www.clinicalkey.es/playcontent/1-s2.0-S1473309913702044>. doi: 10.1016/S1473-3099(13)70204-4.

27. Collard D, Nurmohamed NS, Kaiser Y, et al. Cardiovascular risk factors and COVID-19 outcomes in hospitalised patients: A prospective cohort study. *BMJ Open*. 2021;11(2):e045482. <https://bmjopen.bmj.com/content/11/2/e045482>. Accessed May 16, 2021. doi: 10.1136/bmjopen-2020-045482.

28. Clark CE, McDonagh STJ, McManus RJ, Martin U. COVID-19 and hypertension: Risks and management. A scientific statement on behalf of the british and irish hypertension society. *Journal of human hypertension*. 2021;35(4):304-307. <https://www.ncbi.nlm.nih.gov/pubmed/33483621>. doi: 10.1038/s41371-020-00451-x.

29. A randomized trial of intensive versus standard blood-pressure control. *New England Journal of Medicine*. 2015;373(22):2103-2116. <https://doi.org/10.1056/NEJMoa1511939>. Accessed May 16, 2021. doi: 10.1056/NEJMoa1511939.

30. Patel SK, Juno JA, Lee WS, et al. Plasma ACE2 activity is persistently elevated following SARS-CoV-2 infection: Implications for COVID-19 pathogenesis and consequences. *Eur Respir J*. 2021;57(5). Accessed May 18, 2021. doi: 10.1183/13993003.03730-2020.

# stylefix

# Figures and Tables

**Figure 1** - Flowchart demonstrating the most pertinent features of our COVID-19 cohort. **Abbreviations -** BAME, Black and minority ethnic; COVID-19, Coronavirus; HFrEF, Heart failure with reduced ejection fraction; LVEF, Left ventricular ejection fraction; PASP, Pulmonary artery systolic pressure; PCR, Polymerase chain reaction; RV, Right Ventricle.

**Figure 2** - Bar chart demonstrating the distribution of co-morbdities in both survivors and non survivors. **Abbreviations -** BMI, Body Mass Index.

**Table 1** – Baseline demographics, risk factors, biochemical and echocardiographic parameters.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Summary/category** | **Total (n=87)** | **Survivors (n=36)** | **Non-survivors (n=51)** | **OR** | **P-values** | **95%CI -low** | **95%CI -high** |
| **Age (years)** | Mean/SD | 62.5 ± 14.8 | 64 ± 13.7 | 61.5 ± 15.6 | 1.01 | 0.429 | 0.98 | 1.04 |
|  | Median /(Q1-Q3) | 64 (56-72.5) | 67.5 (55.3-73) | 61 (56-70.5) |  |  |  |  |
|  | Min-Max | 17-92 | 20-86 | 17-92 |  |  |  |  |
| **Gender** | Women | 39 (44.8%) | 19 (52.8%) | 20 (39.2%) |  |  |  |  |
|  | Men | 48 (55.2%) | 17 (47.2%) | 31 (60.8%) | 0.58 | 0.212 | 0.24 | 1.37 |
| **ITU admission** | Non-ITU | 36 (41.4%) | 6 (16.7%) | 30 (58.8%) |  |  |  |  |
|  | ITU | 51 (58.6%) | 30 (83.3%) | 21(41.2%) | 7.14 | **<0.001** | 2.53 | 20.19 |
| **Ethnicity:** | White | 26 (29.9%) | 11 (30.6%) | 15 (29.4%) |  |  |  |  |
|  | Asian | 5 (5.7%) | 3 (8.3%) | 2 (3.9%) |  |  |  |  |
|  | Others | 19 (21.8%) | 8 (22.2%) | 10 (19.6%) |  |  |  |  |
|  | Black | 29 (33.3%) | 10 (27.8%) | 19 (37.3%) |  |  |  |  |
|  | BAME | 53 (60.9%) | 22 (61.1%) | 31 (60.8%) |  |  |  |  |
|  | Missing | 8 (9.2%) | 3 (8.3%) | 5 (9.8%) |  |  |  |  |
| **Ethnicity (binary)** | Caucasians | 26 (29.9%) | 11 (30.6%) | 15 (29.4%) |  |  |  |  |
|  | Non-caucasians | 53 (60.9%) | 22 (61.1%) | 31(60.8%) | 0.97 | 0.946 | 0.37 | 2.50 |
|  | Missing | 8 (9.2%) | 3 (8.3%) | 5 (9.8%) |  |  |  |  |
| **BMI (kg/m2)**  | Mean/SD | 29.8 ± 6.9 | 30.8 ± 8.2 | 29.2 ± 6.1 | 1.03 | 0.339 | 0.96 | 1.11 |
|  | Median /(Q1-Q3) | 28.4 (25.5-32.8) | 29.4 (26.5-33.7) | 28.4 (25.2-32.4) |  |  |  |  |
|  | Min-Max | 17.9–54.7 | 19.6-54.7 | 17.9-46.2 |  |  |  |  |
|  | Missing | 15 (17.2%) | 10 (27.8%) | 5 (9.8%) |  |  |  |  |
| **Comorbidities:** | Hypertension |  |  |  |  |  |  |  |
|  | NO | 42 (48.3%) | 13 (36.1%) | 29 (56.9%) |  |  |  |  |
|  | YES | 45 (51.7%) | 23 (63.9%) | 22 (43.1%) | 2.33 | 0.059 | 0.97 | 5.61 |
|  | Diabetes mellitus |  |  |  |  |  |  |  |
|  | NO | 58 (66.7%) | 24 (66.7%) | 34 (66.7%) |  |  |  |  |
|  | YES | 29 (33.3%) | 12 (33.3%) | 17 (33.3%) | 1.00 | 0.999 | 0.40 | 2.47 |
|  | Chronic kidney disease |  |  |  |  |  |  |  |
|  | NO | 68.2%(78.2%) | 30 (83.3%) | 41 (80.4%) |  |  |  |  |
|  | YES | 19 (21.2%) | 6 (16.7%) | 10 (19.6%) | 0.82 | 0.728 | 0.27 | 2.50 |
|  | Coronary artery disease |  |  |  |  |  |  |  |
|  | NO | 77(88.5%) | 31 (86.1%) | 46 (90.2%) |  |  |  |  |
|  | YES | 10 (11.5%) | 5 (13.9%) | 5 (9.8%) | 1.48 | 0.558 | 0.40 | 5.56 |
|  | COPD |  |  |  |  |  |  |  |
|  | NO | 81(93.1%) | 35 (97.2%) | 46 (90.2%) |  |  |  |  |
|  | YES | 6 (6.9%) | 1 (2.8%) | 5 (9.8%) | 0.26 | 0.232 | 0.03 | 2.35 |
|  | Atrial Fibrillation |  |  |  |  |  |  |  |
|  | NO | 78 (89.7%) | 33 (91.7%) | 45 (88.2%) |  |  |  |  |
|  | YES | 9 (10.3%) | 3 (8.3%) | 6 (11.8%) | 0.68 | 0.606 | 0.16 | 2.93 |
|  | Obesity (BMI >30) kg/m2)  |  |  |  |  |  |  |  |
|  | NO | 58 (66.7%) | 25 (69.4%) | 33(64.7%) |  |  |  |  |
|  | YES | 29 (33.3%) | 11 (30.6%) | 18 (35.3%) | 1.14 | 0.792 | .43 | 3.03 |
| **Echocardiographic** **Variables** |  |  |  |  |  |  |  |  |
| LVEF (%)  | Mean/SD | 60.7 ± 10 | 62.1 ± 10.8 | 59.8 ± 9.5 | 1.03 | 0.296 | 0.98 | 1.08 |
|  | Median/(Q1-Q3) | 62.8 (57.5-65) | 65 (60-67.5) | 62.5 (57.5-65) |  |  |  |  |
|  | Range (Min-Max) | 12.5-75 | 12.5-75 | 17.5-68 |  |  |  |  |
|  | Missing | 1 (1.1%) | 0 | 1 (1.9%) |  |  |  |  |
| Left Ventricle size (cm) | Mean/SD | 4.4 ± 0.6 | 4.2 ± 0.7 | 4.6 ± 0.5 | 0.37 | **0.019** | 0.16 | 0.85 |
|  | Median/(Q1-Q3) | 4.5 (4-4.8) | 4.2 (3.9-4.6) | 4.6 (4.3-4.9) |  |  |  |  |
|  | Range (Min-Max) | 2.8-6.2 | 2.8-6.2 | 3.3-5.7 |  |  |  |  |
|  | Missing | 2 (2.3%) | 0 | 2 (3.9%) |  |  |  |  |
| Left Atrial Size (cm) | Mean/SD | 3.6 ± 0.7 | 3.3 ± 0.6 | 3.7 ± 0.7 | 0.40 | 0.082 | 0.14 | 1.12 |
|  | Median/(Q1-Q3) | 3.6 (3.1-3.9) | 3.4 (3.1-3.7) | 3.7 (3.3-4) |  |  |  |  |
|  | Range (Min-Max) | 1.7-5.6 | 1.7-4.5 | 2.7-5.6 |  |  |  |  |
|  | Missing | 36 (41.4%) | 20 (55.6%) | 16 (31.4%) |  |  |  |  |
| Right Ventricle size (cm) | Mean/SD | 4.0 ± 0.8 | 4.0 ± 0.8 | 3.9 ± 0.8 | 1.53 | 0.531 | 0.40 | 5.86 |
|  | Median/(Q1-Q3) | 4.3 (3.5-4.7) | 4.3 (4.1-4.8) | 4.1 (3.5-4.5) |  |  |  |  |
|  | Range (Min-Max) | 2.4-5 | 2.4-5 | 2.6-5 |  |  |  |  |
|  | Missing | 71 (81.6%) | 30 (83.3%) | 41 (80.4%) |  |  |  |  |
| Right atrial area (cm2) | Mean/SD | 16.4 ± 5.7 | 14.8 ± 3.4 | 17 ± 6.4 | 0.92 | 0.361 | 0.77 | 1.10 |
|  | Median/(Q1-Q3) | 14.9 (13-19.3) | 14.7 (13.1-17) | 14.9 (13-21.1) |  |  |  |  |
|  | Range (Min-Max) | 7.7-34.7 | 8.8-20.2 | 7.7-34.7 |  |  |  |  |
|  | Missing | 59 (67.8%) | 28 (77.8%) | 31 (60.8%) |  |  |  |  |
| PASP (mmHg) | Mean/SD | 41.7 ± 13.1 | 44.5 ± 14.2 | 38.5 ± 11.1 | 1.04 | 0.134 | 0.99 | 1.09 |
|  | Median/(Q1-Q3) | 40 (32.1-49.9) | 42.5 (35.5-52) | 35.5 (32-44) |  |  |  |  |
|  | Range (Min-Max) | 21.5-77 | 22.5-77 | 21.5-61 |  |  |  |  |
|  | Missing | 38 (43.7%) | 11 (30.6%) | 27 (52.9%) |  |  |  |  |
| Right ventricular dysfunction | NO | 64 (73.6%) | 22 (61.1%) | 42 (82.4%) |  |  |  |  |
|  | YES | 23 (26.4%) | 14 (38.9%) | 9 (17.6%) | 2.97 | **0.030** | 1.11 | 7.94 |
|  | Missing | 0 | 0 | 0 |  |  |  |  |
| Elevated PASP | NO | 17 (19.5%) | 7 (19.4%) | 10 (19.6%) |  |  |  |  |
|  | YES | 32 (36.8%) | 18 (50.0%) | 14 (27.5%) | 1.84 | 0.317 | 0.56 | 6.05 |
|  | Missing | 38 (43.7%) | 11 (30.6%) | 27 (52.9%) |  |  |  |  |
| Impaired LVEF | NO | 79 (90.8%) | 33 (91.7%) | 46 (90.2%) |  |  |  |  |
|  | YES | 7 (8.0%) | 3 (8.3%) | 4 (7.8%) | 1.045 | 0.956 | 0.22 | 4.99 |
|  | Missing | 1 (1.1%) | 0 | 1 (2.0%) |  |  |  |  |
| **Biomarkers** |  |  |  |  |  |  |  |  |
| Troponin (ng/L)  | Median /(Q1-Q3) | 58.6 (9.8-97.1) | 71.2 (17.5-97.6) | 45.3 (8.9-97.1) | 1.14 | 0.316 | 0.88 | 1.47 |
| (log scale used in analysis) | Mean/SD | 268.3 ± 826.9 | 226.7 ± 384.6 | 299.2 ± 1049.5 |  |  |  |  |
|  | Range (min-max) | 1.1 – 6958 | 4.2-1439.7 | 1.1-6958 |  |  |  |  |
|  | Missing | 6 (6.9%) | 1 (2.8%) | 5 (9.8%) |  |  |  |  |
| **Confirmed Pulmonary Embolism** | NO | 16(18.4%) | 7(19.4%) | 9(17.7%) |  |  |  |  |
|  | YES | 4 (4.6%) | 1 (2.8%) | 3 (5.9%) | 0.43 | 0.501 | 0.0362752 | 5.06 |
|  | Missing | 67(77%) | 28(77.8%) | 39(76.5%) |  |  |  |  |

Data is presented as mean ± standard deviation, median (Q1-Q3) and number (%)

**Abbreviations:** BAME, Black and minority ethnic; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ITU, intensive care unit; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure.