A Comparative Study of the Right Heart Echocardiography Findings in COVID-19 and Non-COVID-19 Pneumonia in a South African Population

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Title

A comparative study of the right heart echocardiography findings in COVID-19 and non-COVID-19 pneumonia in a South African population

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Abstract:

Introduction

The right ventricle is affected by Coronavirus disease 19 (COVID-19) via multiple mechanisms, which can result in right ventricular dysfunction (RVD), portending a poorer prognosis than those without RVD. There is a paucity of data regarding right ventricular function in COVID-19 pneumonia from Africa and therefore in this comparative study of COVID-19 and non- COVID-19 pneumonia,

we aimed to provide a detailed assessment of right heart function using conventional echocardiography and advanced strain imaging.

Methods

This study was an observational, prospective, single-centre study, including adults with hypoxic pneumonia, in two groups: COVID-19 pneumonia; and non-COVID-19 community acquired pneumonia (CAP). Bedside echocardiography was performed according to a pre-specified protocol and all right heart measurements were done as per standard guidelines. Right ventricular free wall strain (RVFWS) was measured using Philips® QLAB 11.0 speckle tracking software.

Results

We enrolled 48 patients with COVID-19 pneumonia and 24 with non-COVID-19 CAP. COVID-19 patients were significantly older, with a median age of 52 years (IQR 42-62.5, p=0.006), with fewer HIV positive patients, 25% versus 54% (p=0.01), and a higher frequency of hypertension and diabetes. There was a trend towards a lower severity of illness score (SAPS II). Median Tricuspid Annular Plane Systolic Excursion (TAPSE) and RVS' were not significantly different between COVID-19 and CAP . Mean RVFWS yielded the highest estimates for prevalence of RVD; 81% (CI 75-87%, n=43) amongst COVID-19 pneumonia patients and 79% (CI 71-87%, n=24) for CAP . Non-COVID patients with moderate to severe hypoxemia (PF<150) were at greater risk of an elevated RVSP >30mmHg RR= 3.25 (CI 1.35-7.82) on admission.

Conclusion

Despite a clinically significantly lower severity of illness score, patients with COVID-19 pneumonia had a similar admission prevalence of RVD when compared to patients with non-COVID CAP . COVID-19 pneumonia patients had mortality that was significantly higher than predicted mortality. Additionally, despite preserved traditional parameters of RV systolic function, RVFWS was diminished in both groups, thus RVFWS served as an important marker of subclinical disease of RV.

Keywords:

COVID-19

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Word count: 329

Introduction

The right ventricle is affected by Coronavirus disease 19 (COVID-19) by multiple mechanisms, including cardiac and systemic inflammation, volume status, increased sympathetic tone, direct cardiac involvement by severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2), thrombosis (including micro-thrombosis and macro-thrombosis) altering the ventilation-perfusion matching resulting in ventilation/perfusion mismatching, hypoxia from shunting and atelectasis[1, 2], and hypoxic pulmonary vasoconstriction increasing right ventricular (RV) afterload. This can cause acute cor pulmonale, cardiogenic shock, thrombotic events and complications, acute coronary syndromes, myocardial injury, and arrhythmias[3-5]. Findings on transthoracic echocardiography of hospitalised COVID-19 patients relevant to the right heart include increased pulmonary arterial pressures (PAP)[4, 6]; RV dilatation[6-8]; and RV dysfunction[6, 7]. Mortality in severe COVID-19 pneumonia with a diagnosis of RV dysfunction (RVD) is increased compared to those without RVD[9].

There has been a high incidence of venous thromboembolism described in COVID-19 [10-12], often despite thromboprophylaxis administration [13], with microthrombi found in small lung arteries [14], and a raised d-dimer in non-survivors compared to survivors [15]. There is increased arterial thrombosis manifesting as an increased rate of acute myocardial infarction [16]. The vasculopathy of the lung likely manifests in ventilation/perfusion mismatching and contributes to the hypoxaemia seen in COVID-19 pneumonia [17]. COVID-19 associated diffuse alveolar damage (DAD) has an almost ten-fold greater incidence of capillary microthrombosis than influenza-associated DAD, strongly linking pneumonia to endothelial dysfuction in SARS-Co-V-2[18].

The RVD is caused by COVID-19 sequelae, including hypoxic pulmonary vasoconstriction, which characterises COVID-19 related pneumonia and acute respiratory distress syndrome (ARDS)[19]. Progressive consolidation and atelectasis cause further physical distortion of the pulmonary vessels [20], and thromboembolism and the hypercoagulopathy seen in COVID-19 add additional strain and increase pulmonary arterial systolic pressure (PASP). Furthermore, should the patient receive positive end-expiratory pressure and/or a driving pressure, the afterload to the RV is increased. These mechanisms all contribute to the increased RV strain. Additionally, there is evidence to show that there is direct myocardial involvement by COVID-19[14, 21].

Traditionally RV function has been characterised using Tricuspid Annular Plane Systolic Excursion (TAPSE), the RV fractional area change, and the RV systolic excursion velocity (RVS'), and is a predictive factor of mortality in COVID-19[22], however, RV free wall strain (RVFWS) is a better predictor of mortality than TAPSE and RVS' [22].

There is a paucity of data regarding RV function in COVID-19 pneumonia from Africa and therefore in this comparative study of COVID-19 and non- COVID-19 CAP, we aimed to provide a detailed assessment of right heart function using conventional and advanced strain imaging.

Methods

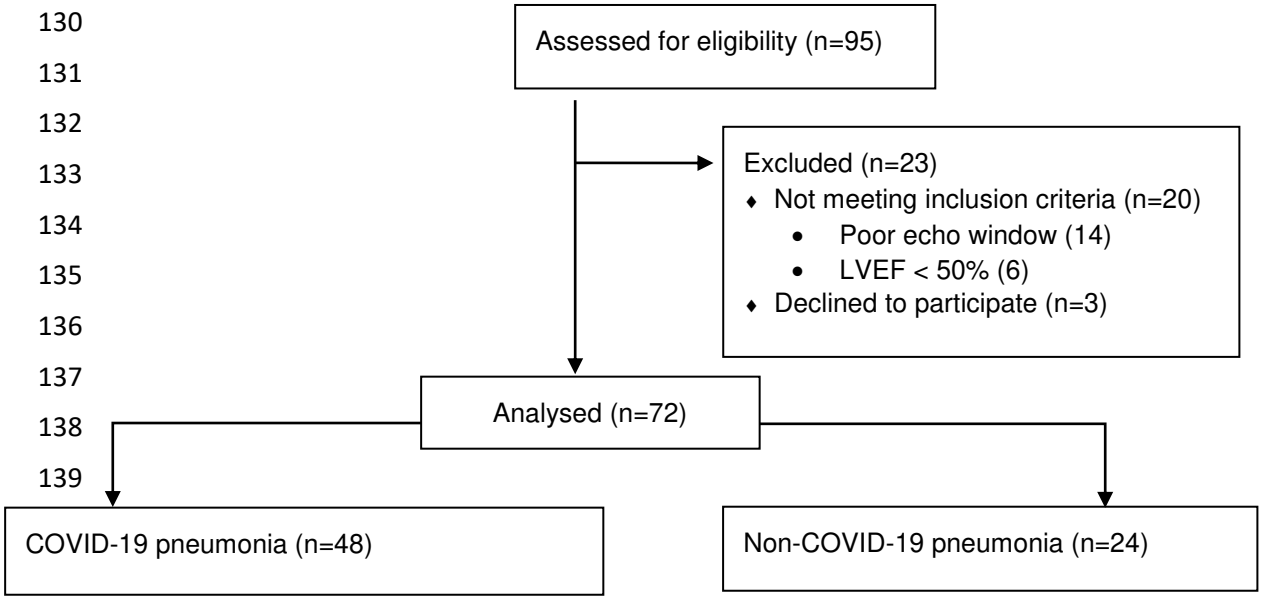
Study design and site

This was a prospective, observational, cohort study of hypoxic pneumonia (COVID-19 pneumonia and non-COVID-19 CAP) in adult patients at Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa.

Study population, inclusion, and exclusion criteria

We screened all consecutive adult patients during working hours of weekdays, who were persons under investigation for SARS-CoV-2 virus, and were admitted between 20 October 2021 and 11 March 2021 were considered for enrolment. Patients were included if they had hypoxic physician-diagnosed or chest x-ray-diagnosed pneumonia and met the criteria for severe disease or critical illness. Severe disease was defined as oxygen saturation ≤92% with a respiratory rate ≥25 and therefore requiring supplemental oxygen support without the need for invasive or non-invasive ventilation. Critical illness was defined as hypoxemia and the need for additional ventilatory support, in the form of non-invasive or invasive ventilation. We excluded patients if they were pregnant, had a known chronic lung disease, chronic cardiac disease, specifically ischaemic heart disease, cardiomyopathy, and valvular heart disease, a known left ventricular ejection fraction (LVEF) less than 50%, or a history of pulmonary or cardiac surgery.

Study participation Flow Diagram



Procedure

All enrolled patients signed informed consent. If the patient was confused, delirious, intubated, or otherwise incapacitated, and the patient could not sign and date the informed consent document, we sought informed consent from the next of kin in a tiered approach.

Patient demographic, clinical, laboratory, and hospital survival data were extracted from clinical notes. The following scores were calculated from the clinical information at the time of admission: simplified acute physiology score 2 (SAPS2)[23] and Sequential Organ Failure Assessment (SOFA) scores[24], and admission biomarkers were recorded. We further classified patients with COVID-19 and non-COVID 19 CAP by a P/F ratio below 150 and ≥ 150.

Two- dimensional echocardiography

Transthoracic echocardiography was performed on all patients in the left lateral position or supine position (ventilated patients) using a S5-1 transducer on a Philips® portable CX 50 system (Amsterdam, the Netherlands). The images were obtained according to a standardized protocol. The data were transferred and analyzed offline using the Philips® Xcelera workstation . In addition to LVEF, the following RV systolic functional parameters were measured: time to peak pulmonary velocity using RV tissue Doppler imaging (TDI) as a surrogate for pulmonary vascular resistance (PVR); and TAPSE; RVS' velocity; right ventricular systolic pressure (RVSP). RV pulse wave Doppler and TDI were performed to assess the RV E/A ratio and E/E' ratio, as a surrogate of RV diastolic function. All measurements relating to the RV were performed by an experienced Cardiologist based on the ASE guidelines on the RV[25].

Right ventricle strain analysis

RV free-wall PSS was derived from a modified A4C RV view. Once three points, namely the RV apex, medial and lateral tricuspid annulus, were defined, the software automatically traced the endocardial and epicardial border. Philips® QLAB version 11.0 software allowed off-line semi-automated analysis of speckle-based strain. This results in the division of the RV into six standard segments in the A4C view. The region of interest, once created, can be manually adjusted as needed to allow for adequate speckle-tracking. The RV free-wall peak systolic strain (PSS) was obtained by averaging three lateral segments (the basal, mid, and apical RV wall). The interventricular septum was excluded from the analysis. The longitudinal ε curves for each segment and a mean curve of all segments were generated by the software. These curves were used to derive peak negative RV free-wall PSS. RV free wall PSS has been shown to be feasible and reproducible in our unit with intra-observer and inter-observer variability coefficient of 7% and 7.6% respectively[26].

Outcome measures

We aimed to describe and compare COVID-19 pneumonia and non-COVID-19 CAP concerning RV function using conventional parameters and strain imaging.

Statistical Analysis

Study data were collected and managed using REDCap® electronic data capture tools hosted at the University of Witwatersrand (Research Electronic Data Capture)[27, 28]. Statistical analyses were performed using Statistica® version 13.3 (TIBCO Software Inc., USA). Continuous variables are expressed as median [interquartile range (IQR)], and proportions/percentages were used for categorical variables. Continuous data were compared using the Mann–Whitney U test while proportions were compared using the chi-square test. A p-value < 0.05 was considered statistically significant. The proportion of pneumonia patients with evidence of right heart strain was <5%. Spearman Rank Order Correlations will be used to determine the correlation between RV parameters and clinical parameters. Using a 90% power and 5% significance level we required a sample size of 36 (18 in each group) to show an increase in the proportion of such patients from 5% to 20%[17]. A sample size of 20 participants with non-COVID-19 pneumonia admitted to the person under investigation (PUI) ward, and 40 participants with COVID-19 pneumonia were required. Assuming a 20% poor image quality rate, a final sample size of 24 non-COVID-19, and 48 COVID-19 pneumonia participants was required.

Ethics considerations

Approval was received from the University Human Research Ethics Committee (Medical), M200728. National Health Research Database GP_202008_140. Written informed consent from the patient or patient surrogate was obtained as per local ethics committee guidelines.

Results

Patient characteristics

We enrolled 48 patients with COVID-19 pneumonia (COVID-19) and 24 with non-COVID-19 pneumonia (CAP). COVID-19 patients were significantly older, with fewer HIV positive patients and a higher frequency of hypertension and diabetes. There was a trend towards a lower severity of illness score (SAPS II) and significantly lower lactate levels amongst the COVID-19 group. The clinical characteristics of the cohort are shown in (Table 1). The median LVEF of the whole cohort was 60% [IQR: 53.6-68.2]. This study focussed on right heart echocardiographic findings, and excluded all patients with a LVEF <50%, in an attempt to exclude right heart abnormalities due to left heart systolic dysfunction.

Among the COVID-19 positive patients enrolled, 30 (62.5%) were classified under as severe type (need for supplemental oxygen) of COVID-19 pneumonia and 18 (37.5%) were classified as critically ill (need for ventilator respiratory assistance), compared to 20 (83.3%) and 4 (16.7%) among COVID negative patients respectively. There was no significant difference between the groups, p= 0.07.

Baseline arterial blood gas and biomarkers are provided in Table 2. Compared to the COVID-19 cohort, the non-COVID-19 cohort had significantly higher d-dimers. Troponin correlated with RV diastolic dysfunction, with Spearman Rank Order Correlations for RV E/A of -0.26, and E/E' of 0.27.

Right ventricular dysfunction in COVID-19 and non-COVID CAP

The echocardiographic parameters are shown in Table 3. COVID-19 pneumonia patients were 2.6 times more likely not to have TR (confidence interval 1.14-6.03) compared to patient with CAP. There was no statistically significant difference in RVSP or RVS' between the COVID-19 positive and negative groups. The relative risk (RR) of non-COVID-19 CAP patients having a PASP >30mmHg was 3.25 times higher compared to COVID-19 patients (CI 1.35-7.82) on admission. Time to peak pulmonary velocity correlates inversely with RVSP, Spearman Rank Order Correlations -0.33, indicating a short time to peak, or a high pulmonary vascular resistance being associated with a high RVSP.

Mean RVFWS yielded the highest estimates for prevalence of right ventricular dysfunction; 81% (CI 75-87%, n=43) amongst COVID-19 pneumonia patients and 79% (CI 71-87%, n=24) for non-COVID CAP . See figure 2 and 3. Average RVFWS correlates positively with RV wall thickness, Spearman Rank Order Correlations 0.33.

Over half (29/48, 60%) of the COVID-19 group had an admission P/F ratio <150 compared to 58% (14/24) of the non- COVID-19 CAP group, p=0.87. Using this group with a P/F ratio <150, RVSP and RVFWS were compared. See table 4 below.

Mortality

Despite a lower SAPS II score and predicted mortality, the COVID-19 group had a significantly higher actual mortality. This was not the case for the non-COVID-19 CAP group. See table 5.

Significant factors on echocardiography associated with mortality were a larger RV, as evidenced by longer RV length, median 66.5mm in non-survivors compared to 59.5mm in survivors (p=0.04).

Regarding the COVID-19 group only, higher troponin (p=0.04), higher SAPS 2 (p=0.02) and SOFA (p=0.02) scores, and lower pH (p=0.01) were found in the non-survivors compared to the survivors. There were no significantly different right heart echocardiography findings between the COVID-19 survivors and non-survivors. See Table 6.

Discussion

The main findings of this study are as follows: 1) Despite a lower severity of illness score, patients with COVID-19 pneumonia had a similar admission prevalence of right ventricular dysfunction when compared to patients with non-COVID CAP; 2) RVFWS was superior to traditional RV parameters for assessing early RV systolic dysfunction; 3) The actual mortality was higher than predicted for COVID-19 pneumonia but not for non-COVID-19 CAP.

COVID-19 patients were significantly older and had a higher frequency of hypertension and diabetes, in keeping with advancing age and metabolic phenotype being known risk factors for infection and morbidity of COVID-19[29]. The COVID-19 group had a lower HIV positivity rate than the non-COVID-19 CAP group, not in keeping with a large South African cohort which demonstrated a similar positivity rate amongst COVID-19 and CAP patients[30], however, the study was based in a different geographical location of the country, serving a different population group, and the contribution of other comorbidities could alter the results. There was a trend towards a lower severity of illness score (SAPS II) amongst the COVID-19 group, which, although not statistically different due to small numbers, is clinically significant, as the median SAPS II of 29 in non-COVID-19 patients indicated more than one organ involvement. COVID-19 negative CAP patients had significantly higher d-dimer levels and higher lactate than their COVID-19 counterparts. Both groups had similar numbers of patients with severe ARDS, (P/F ratio <100 in 27% COVID-19 and 29% non-COVID-19 CAP), a similar proportion of severe ARDS as that described by an Italian study[31], and overall oxygenation impairment was equal in both groups. This is in comparison to a Turkish study which described exclusively critically ill patients and showed no difference between genders and age, and the SOFA scores of the COVID-19 group and the non-COVID-19 CAP group were comparable (7 and 8 respectively), and the APACHE II was the same (21)[32].

Median RV systolic function defined by TAPSE, RVS' and PASP were preserved (Table 3), and not significantly different between the COVID-19 and non-COVID-19 CAP cohorts. An early echocardiography low-normal (<18) TAPSE is associated with mortality within patients who are hospitalised with COVID-19 pneumonia[33], a finding not present in the current study, in keeping with the finding that RVFWS is a better marker of RV dysfunction than TAPSE. A significantly higher proportion of patients were identified as having RV dysfunction by mean RVFWS than by TAPSE, RVS' and PASP within each cohort. In critically ill patients, increased PASPs have been reported with a prevalence ranging from 29% [4] to 69.5%[6], and in another cohort up to 76% for those mechanically ventilated[34]. The cut-off for elevated PASP varied between 25-40mmHg.

Non-COVID-19 CAP patients had higher PASP and larger RV than the COVID-19 cohort on admission. The possible reasons for this include a more severely ill cohort with more organ dysfunction at time of admission (as shown by the severity scores) and a higher HIV prevalence with a potential contribution to pre-existing pulmonary hypertension within the non COVID-19 CAP group. Further, the trajectory of COVID-19 pneumonia is of disease progression over time, to become a multi-system disease with micro-thrombosis and inflammation, hence admission presentation may be considerably less severe with subsequent disease progression.

The COVID-19 cohort had a lower limit of normal RV diastolic relaxation. The E/E' was not different between the COVID-19 and non-COVID-19 CAP cohort. This is in keeping with Zhang *et al*. who demonstrated normal RV E/A and E/E', both in controls and in the COVID-19 groups[35]. There was no difference between the right atrial size between the two groups, and the overall RA size was normal, and there was no evidence of restrictive filling (a tricuspid E/A ratio > 2.1 with a deceleration time < 120 ms). IVC diameter was normal in the two groups, but significantly lower in the COVID-19 group. This difference could be accounted for by a decreased volume status in this group, or it could be a random difference, with many factors influencing this finding. Elevated troponin correlated positively with impaired diastolic relaxation, implying subendocardial ischaemia, caused by a range of possible aetiologies, including, but not limited to hypoxia, stress, shunting, lung atelectasis, and the application of positive end-expiratory pressure. There is little data on RV diastolic dysfunction with which to compare the findings of the current study. The RV diastolic compliance is more pronounced than the LV, contributing to adaptations in preload[36].

RV dilation is among the most common echocardiography findings, with a prevalence of between 28%[6] and 74%[37], and patients with RV dilation have been shown to have a four time increase in mortality rate compared to those without RV dilation[8].

RV dysfunction, described as independently associated with mortality[38], with a reported prevalence ranging from 27% in patients admitted to critical care[6, 7] to 82%[37] among all hospitalised patients, was found in this study to occur with a prevalence of 81%, however, this was not statistically different from non-COVID-19 CAP patients with hypoxic pneumonia. We propose that this phenomenon is due to the early occurrence of hypoxia in the COVID-19 disease course, compared to the later presentation of hypoxia which is seen in non-COVID-19 CAP, by which time the patients have multi-organ involvement and higher disease severity scores.

RVFWS was found to be a more sensitive indicator of RV systolic dysfunction than RVS' or TAPSE. RVFWS assessment is less impacted by cardiac motion, the left ventricle, and the volume status[39, 40], and gives both regional (apex, mid-section, and base) and global assessments, and hence is a good

measurement of RV dysfunction. In the current study, mean RVFWS yielded the highest estimates for the prevalence of RV dysfunction; 81% (CI 75-87%, n=43) amongst COVID-19 pneumonia patients. This was in a cohort of COVID-19 hypoxic patients with median SAPS2 of 18, and SOFA of 2. It is difficult to ascertain the true degree of RVD that occurs in COVID-19 hypoxic pneumonia due to the heterogeneity in the literature of disease severity (supplemental oxygen requiring vs invasive mechanically ventilated or receiving ECMO, varying P/F ratios), clinical settings (hospitalised vs intensive care), and variability in the timing of echocardiography with regard disease progression, however, the prevalence of RVFWS is reported to vary between 22.7%[35], 35%[41] and up to 66%[42] in ventilated COVID-19 patients. We found mean RVFWS strain correlates positively with RV wall thickness.

RV longitudinal strain was found in 24.2% of non-COVID-19 patients and 19.8% in COVID-19 CAP patients in a Danish study where patients were well matched for age and body mass index, but not for diabetes and dyslipidaemia, both occurring with increased frequency amongst the COVID-19 group[43]. The prevalence of RV strain in these studies is different from our current study and may suggest a more severely ill cohort in the current study, and differences in the timing of imaging.

Interestingly, there is a longitudinal study showing RV speckle-tracking echocardiography parameters improve with the resolution of COVID-19 symptoms, with RVFWS occurring in 23% of hospitalised patients, and only 8% at follow up post discharge[44]. The current study did not perform serial echocardiography but suggests that hypoxia (from both shunting and V/Q mismatch) contributes to acute RVFWS and dysfunction, and improves with the resolution of hypoxia.

The mortality rate for COVID-19 was high (27%) compared to non-COVID-19 CAP (12%). Most of our critically ill COVID-19 patients requiring invasive mechanical ventilation IMV received non-invasive ventilator support before intubation, which could bias the cohort toward more severely ill patients.
The standardised mortality rate (SMR) indicates that the actual mortality was higher than predicted for COVID-19 pneumonia but not for non-COVID-19 CAP, despite the two groups being similar in terms of oxygenation, LV function, and prevalence of RV dysfunction, and the COVID-19 group having a clinically significantly lower SAPS II score.

A Spanish study described 742 COVID-19 patients with ARDS, and their cohort had a median SOFA score of 6, with a predicted mortality of <33.3%[45], and an actual 28 day mortality of 32%[46]. An Italian study[47] described an older cohort of COVID-19 patients with respiratory failure and compared them to a historical cohort, and showed a SOFA of 8 amongst the COVID-19 cohort, with a predicted in-hospital mortality of <33.3%[45], and an actual mortality of 63%, compared to the non-COVID-19 CAP

cohort, with median SOFA of 14, who had an actual mortality of 30% despite a predicted in-hospital mortality of >95.2%[45]. Despite no formal severity scores, a Chinese study demonstrated mortality among patients with acute lung injury admitted to ICU to be 57.8% among the COVID-19 cohort, and 35.4% among the non-COVID-19 cohort, despite the COVID-19 cohort being younger and having fewer comorbidities[48]. This mirrors the higher mortality observed within this study among the COVID-19 group, despite the non –COVID-19 CAP group having a higher SAPS II score, higher lactate, and a greater proportion of HIV positivity, reflecting the severity COVID.

RVFWS was found to be predictive of mortality in both COVID-19 and non-COVID-19 in the current study, signifying that diminished (more positive or less negative value). RVFWS is a poor prognostic feature, regardless of aetiology (COVID-19 or non-COVID-19). This was corroborated with a study from Li *et al.* that RVFWS was a better predictor of mortality than TAPSE and RVS'[22].

Troponin was significantly higher in all-cause non survivors and in COVID-19 non-survivors, and CRP and d-dimers trended higher, suggesting a prominent role of myocardial injury within the non-surviving group, in keeping with international literature associating troponin leakage to poor prognosis[21, 49]. Within the COVID-19 group, myocarditis, micro- and macro-vascular dysfunction, and the resultant cytokine storm, and the development of pulmonary emboli, contribute to myocardial dysfunction and the troponin leakage[50]. An elevated troponin has been positively correlated with RV dysfunction and normal LV function in COVID-19 infection, although this study did not comment on strain[51]. In a study of 35 patients, RV strain was found to be a predictor of outcome, and likely due to the small size of this pilot study, only showed a trend toward higher troponins in patients with more negative strain[52]. Increased CRP has been established in an early metanalysis to be associated with increased severity of COVID-19[53], and a later met analysis confirmed increased elevated cardiac troponin I to be a predictor of mortality within COVID-19[54], a finding confirmed in the present study.

The two groups had similar levels of hypoxaemia as reflected in the P/F ratios, and the non-COVID-19 CAP group was more severely ill with clinically significantly higher severity scores (not reaching statistical significance likely due to low numbers). The two groups had the same prevalence of right ventricular dysfunction, suggesting that the COVID-19 group, who had less multi-organ involvement, as indicated in the severity scores, had a greater risk of high pulmonary pressures. We postulate that the excess risk seen in the COVID-19 group is possibly due to endothelial dysfunction. The endothelial dysfunction causes in-situ platelet aggregation and immunothrombosis, and pulmonary angiopathy[18, 55], causing hypoxia and a dysregulated pulmonary circulation, in addition to impaired RV contractility, contributing to the development of RV dysfunction and RVFWS.

The high prevalence of RVD can be explained by similar and profound levels of hypoxia (mean P/F ratio in both groups less than 150), but these levels of hypoxaemia may occur at different phases of disease between the COVID-19 and non-COVID-19 groups. Hypoxia typically occurs early in the disease course of COVID-19, with the systemic inflammation and multi-organ involvement occurring later, compared to community acquired non-COVID-19 pneumonia, where the profound level of hypoxia occurs later in tandem with multi-organ dysfunction.We postulate that COVID-19 progresses from admission (when our measurements were taken), from predominantly respiratory and hypoxic pneumonia, to a multi-system thrombo-inflammatory disease, causing multi-organ dysfunction, contributing to the high mortality seen despite the predicted mortality. Further, it may be postulated that early RVD in COVID-19 patients portend a poorer prognosis than later RVD.

A recent study looked at 32 mechanically ventilated patients with COVID-19 pneumonia and described a cohort where two-thirds of the patients had abnormal RV strain, and these patients had higher lung compliance and lower plateau pressure[42]. Furthermore, the patients who displayed abnormal strain did not have worse oxygenation, suggesting a role for an alternative insult beyond pressure, pulmonary mechanics, alveolar damage, and hypoxia[42].

Limitations

This study was conducted at a single centre, with a small sample size, and is not necessarily generalizable. Echocardiography is operator dependent, however, this study aimed to mitigate this by having the cardiologist blinded to the clinical details and COVID-19 status of the patient.
The pressures in the right heart as measured on transthoracic echocardiography were not assessed or compared with right heart catheterisation. Patients had some degree of respiratory distress, and as such, intra-thoracic dynamics affect various findings, in particular the IVC collapsibility.
The COVID-19 group had more co-morbidities, were older and were more likely to have a higher BMI and heart failure with preserved ejection fraction. We did not measure pro-BNP and did not exclude these patients. We excluded patients with LV systolic dysfunction but not diastolic dysfunction, which in turn was not systematically studied in all these patients.

Conclusions

Despite an equal overall oxygenation impairment in both COVID-19 and non-COVID-19 pneumonia groups, both groups had a high, and equal prevalence of RV dysfunction. The non-COVID-19 group had higher PASP and bigger RV. Despite a lower severity of illness score, patients with COVID-19 pneumonia had a worse than expected mortality. This leaves an unanswered question of what is responsible for the RV dysfunction within the COVID-19 pneumonia group, and we suggest that

consideration should be given to whether the endothelialitis that is a part of COVID-19 coagulopathy contributes to this dysfunction

Total words: 4284

List of abbreviations used

A	peak velocity flow in late diastole caused by atrial contraction
ARDS	acute respiratory distress syndrome
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	confidence interval
COVID-19	Corona virus disease 2019
CXR	Chest X-ray
DAD	diffuse alveolar damage
E	ratio of peak velocity blood flow from left ventricular relaxation in early diastole
GGO	ground glass opacification
HIV	human immunodeficiency syndrome
IQR	interquartile range
IVC	inferior vena cava diameter
LVEF	left ventricular ejection fraction
P/F	Horowitz Index for Lung Function: ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2) expressed as a fraction
PUI	person under investigation for COVID-19
RV	right ventricle
RVFWS	right ventricular free wall strain
RVD	right ventricular dysfunction
RVS'	right ventricular systolic excursion velocity
RVSP	estimated right ventricular systolic pressure
SAPS II	simplified acute physiology score 2
SOFA	Sequential Organ Failure Assessment
TAPSE	Tricuspid Annular Plane Systolic Excursion

Declarations:

- Ethical Approval and Consent to participate

Approval was received from the University Human Research Ethics Committee (Medical), M200728. National Health Research Database GP_202008_140. Written informed consent from the patient or patient surrogate was obtained as per local ethics committee guidelines.

Consent for Publication

All authors give consent to the publication of this manuscript. This journal article forms part of the first authors PhD thesis, and as such, will be submitted to the University of Witwatersrand as part of the final thesis in submissible format. This article forms part of the first authors PhD thesis.

- Availability of data and materials

Anonymised supporting data will be made available upon request, and is available in an excel spreadsheet

- Competing interests

No author has any conflict of interest to declare.

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Authors' Contributions:

SAVB: conception, design of the work, data collection and sample collection, interpretation of data, drafted the work, substantively revised it, and approved the submitted version, and agrees both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

CNM: conception, design of the work, substantively revised it, and approved the submitted version, and agrees both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

BFJ: conception, design of the work, substantively revised it, and approved the submitted version, and agrees both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

SO: conception, design of the work, analysis and interpretation of data, substantively revised it, and approved the submitted version, and agrees both to be personally accountable for the author's own

contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

RM: design of the work, data collection and sample collection, interpretation of data, drafted the work, substantively revised it, and approved the submitted version, and agrees both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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712 **Table 1: Patient profile**

	Total	Non-COVID-19 pneumonia	COVID-19 pneumonia	p-value
Variable	Mean(SD)/Median [IQR], n=72	Mean(SD)/Median [IQR], n=24	Mean(SD)/Median [IQR], n=48	
Age (years)	49 (13.6)	42.9(11.6)	52 (42-62.5)	0.006*
Female, n (%)	40/72 (56)	12/24 (50)	28/48 (58)	0.5
Co-morbidities (%)				
HIV	25/72 (35)	13/24 (54)	12/48 (25)	0.01*
Hypertension	30/72 (42)	4/24 (17)	26/48 (54)	0.002*
Diabetes	11/70 (16)	2/24 (8)	9/48 (19)	0.04*
Renal	2/72 (2.8)	1/24 (4.2)	1/48 (2.1)	0.61
Other[#]	20/72 (28)	6/24 (25)	14/48 (29)	0.71
Smoker	15/72 (21)	7/24 (29)	8/48 (17)	0.21
SAPS II	21[14-34]	29[17-36.5]	18[13-31.5]	0.15
SOFA	2[2-4]	2.5[2-4]	2[2-4]	0.36
Lactate mmol/L	1.8 [1.2-2.4]	2.2 [1.7-3.2]	1.6 [1.1-2.4]	0.03*

713 SD standard deviation, n number, HIV human immunodeficiency syndrome, SAPSII simplified acute physiology score 2,
714 SOFA Sequential Organ Failure Assessment
715 * Statistically significant
716 [#] Half of the Other group were obese in the COVID-19 group and none were obese in the Non COVID group.
717

718

Table 2: Admission blood gas variables and biomarkers

	All		Non COVID-19 pneumonia			COVID-19 pneumonia	p-value
Variable	**n**	**Mean(SD)/ Median [IQR]**	**n**	**Mean(SD)/ Median [IQR]**	**n**	**Mean(SD)/ Median [IQR]**	
$Pa0_2$ mmHg	72	45 [31-62]	24	43 [29-57]	48	46 [32-63]	0.47
Fi02	72	0.33 [0.21-0.6]	24	0.21 [0.21-0.5]	48	0.4 [0.21-0.60]	0.14
P/F ratio	72	132 [93-192]	24	143 [96-218]	48	126 [81-183]	0.62
pH	72	7.43 [7.40-7.46]	24	7.42 [7.38-7.45]	48	7.44 [7.40-7.46]	0.38
$PaC0_2$ mmHg	60	37 (7.4)	24	36 (9.4)	45	37 (8.5)	0.83
BE meq/L	70	0.3 [-3.0-3.9]	24	-2.7 [-4.1-3.9]	46	1.3 [-1.5-4.0]	0.13
CRP mg/L	72	128 [60.5-211]	24	106 [63-225]	48	132.5 [56-192]	0.92
d-dimer mg/L	66	1.15 [0.38-3.56]	21	2.08 [1.08-3.84]	45	0.82 [0.35-3.18]	0.02*
Troponin ng/L	62	8 [5-20]	16	9 [5-19]	46	7 [5-21]	0.65

[IQR] interquartile range with median, (SD) standard deviation with mean , CRP C reactive protein, PaO_2 partial pressure of oxygen, FiO_2 fraction of inspired oxygen, P/F Horowitz index for Lung Function (P/F ratio) , $PaCO_2$ partial pressure of carbon dioxide, BE base excess

* Statistically significant

Table 3: Echocardiography findings

Variables	n	All	n	COVID-19 pneumonia	n	Non-COVID-19 pneumonia	P value
Time to peak pulmonary velocity (ms)	71	99 [83-117]	47	99 [83-112]	24	93.5 [83-144]	0.62
TAPSE (mm)	72	17.4 [15.2-21.8]	48	17.2 [14.9-21.6]	24	17.8 [16.2-22.2]	0.29
RVSP (mmHg)	53	10 [10-23]	32	10 [10-17.7]	21	15 [7-25]	0.75
RVS' (cm/s)	72	12 [10-14.5]	48	12 [9.8-14.9]	24	12.1 [10.2-13.0]	0.86
E velocity cm/s	72	54.17 (±16.44)	48	53.29 (±15.89)	24	55.93(±17.71)	0.52
A velocity cm/s	71	61.09 (±18.83)	48	63.98 (±17.91)	23	55.05 (±19.65)	0.06
E/A	71	0.84 [0.72-1.14]	48	0.83 [0.69-0.99]	23	1.12 [0.76-1.54]	0.02*
E' velocity cm/s	70	10.42 (±2.96)	46	9.70 (±2.36)	24	11.82 (3.51)	0.003*
A' velocity cm/s	71	14.2 [11.5-16.5]	47	13.8 [11.5-15.8]	24	14.7 [11.4-17.6]	0.69
E/E'	70	5.32 [3.99-6.63]	46	5.44 [4.29-7.04]	24	4.56 [3.61-6.34]	0.21
RV free wall strain (%)	68	-14.4 [-18.9 to -9.7]	44	-14.6 [-18.8 to -10.5]	24	-12.9 [-19.3 to -9.1]	0.97
RV wall thickness (cm)	69	0.60 [0.56-0.74]	45	0.60 [0.54-0.67]	24	0.72 [0.58-0.81]	0.04*
RV base diameter (mm)	69	31.4 [27.4-36.2]	45	31.6 [27.1-36.8]	24	30.3 [27.5-35.2]	0.70
RV longitudinal diameter (mm)	69	60.5 [53.4-67.5]	45	58.7 [51.7-67.2]	24	65.5 [56.8-68.5]	0.08
Tricuspid annular size	70	28.97 (±5.02)	47	28.54 (±4.9)	23	29.83 (±5.3)	0.32
IVC diameter (mm)	69	11.2 [9-13.8]	45	10.2 [8.6-12.1]	24	13.3 [9-15.3]	0.03*
RA major dimension (mm)	70	41.8 (±7.1)	46	42.3 (±7.1)	24	40.8 (±7.1)	0.42
RA minor dimension (mm)	69	35.4 (±7.2)	46	34.4 (±6.6)	23	37.4 (±8.1)	0.10

* Statistically significant , [IQR] interquartile range with median, (SD) standard deviation with mean, interquartile range, ms milliseconds, mm millimetres, mmHg millimetre mercury, n number, TAPSE Tricuspid Annular Plane Systolic Excursion, RVSP right ventricular systolic pressure, RVS' right ventricular systolic excursion velocity, cm/s centimetre per second, E E wave, A A wave, RV right ventricular, IVC inferior vena cava

733 **Table 4: Comparison of RVFWS in COVID-19 patients and non-COVID patients**

Patient Group	RVFWS	COVID-19	Non-COVID	P value
All	RV strain	35	19	
	No RV strain	8	5	0.82
P/F<150	RV strain	20	10	
	No RV strain	6	4	0.7
P/F≥150	RV strain	15	10	
	No RV strain	2	0	0.39

734 RVFWS right ventricular free wall strain, P/F Horowitz index for Lung Function (P/F ratio)

735 **Table 5: Mortality**

	COVID-19 pneumonia (n=48)	Non-COVID-19 pneumonia (n=24)
SAPS II score	18	29
Predicted mortality (95% CI)	2.9% (0.5% - 5.3%)	9.7% (3.7% - 15.7%)
Actual mortality	27.1% (13/48)	12.5% (3/24)
SMR (95% CI)	9.3 (5.1 - 54.2)	1.3 (0.8 - 3.4)

736 SAPSII simplified acute physiology score 2, CI= Confidence intervals, SMR = Standardised mortality ratio

737

738 **Table 6: Factors associated with mortality**

Variables	All survivors	All non-survivors	P value	COVID-19 survivors	COVID-19 non-survivors	P value
Time to peak pulmonary velocity (ms)	93 [83-117]	101 [90-114.5]	0.85	96.5 [88-112]	99.0 [90.0-112.0]	0.99
TAPSE (mm)	17.6 [15.6-21.9]	16.6 [14.15-21.15]	0.23	17.4 [15.3-22]	15.6 [14.0-21.0]	0.14
RVSP (mmHg)	10 [7-23]	10 [10-24]	0.42	10 [10-20.3]	10.0 [10.0-14.0]	0.77
RVS' (cm/s)	12.0 [10.2-13.4]	12.3 [9.15-17.05]	0.55	12.0 [9.6-13.8]	12.7 [10.4-16.9]	0.37
E (m/s)	53.92 (±16.78)	55.05 (±15.67)	0.81	52.3 (±15.9)	56.0 (±16.2)	0.55
A (m/s)	58.87 (±17.73)	68.69 (±21.04)	0.35	61.1 (±17.2)	71.8 (±18.1)	0.53
E/A	0.85 [0.75-1.16]	0.82 [0.61-1.09]	0.23	0.84 [0.72-1.07]	0.80 [0.6-0.88]	0.37
E’	10.53 (±3.00)	10.02 (±2.89)	0.93	9.8 (±2.3)	9.5 (±2.5)	0.53
A’	13.8 [11.3-15.8]	15.1 [12.6-199]	0.21	13.4 [11.3-15.7]	15.1 [12.7-18.2]	0.29
E/E'	5.30 [3.83-6.58]	5.47 [4.06-7.91]	0.46	5.4[4.0-6.6]	5.7 [5.0-8.1]	0.33
RVFWS (%)	-13.48 (±7.08)	-16.31 (±5.88)	0.43	-13.5 (±7.5)	-15.6 (±6.2)	0.25
RV wall thickness (cm)	0.60 [0.57-0.75]	0.6 [0.51-0.68]	0.36	0.6 [0.54-0.69]	0.6 [0.55-0.63]	0.78
RV base (mm)	31.4 [27.4-36.8]	30.2 [26.96-35.9]	0.77	31.6 [27.4-39.3]	28.2 [26.2-35.6]	0.39
RV length (mm)	59.5 [51.7-66.6]	66.5 [57.5-74.35]	0.04*	58.0 [41.1-64.7]	61.0 [56.8-68.5]	0.14
Tricuspid annular size (mm)	29.52 (±4.90)	27.11 (±5.16)	0.74	29.4 (±4.6)	26.2 (±5.0)	0.18
IVC diameter (mm)	11.4 [9.00-13.80]	10.2 [8.5-13.85]	0.76	10.3 [8.8-12.1]	10.2 [8.0-13.1]	0.78
RA length (mm)	42.01 (±7.54)	25.54 (±5.36)	0.16	43.0 (±7.5)	40.4 (±5.9)	0.19
RA width (mm)	35.73 (±7.22)	40.96 (±5.41)	0.92	35.2 (±6.6)	32.4 (±6.3)	0.19
CRP mg/L	122 [58-193.5]	137.5 [79.5-244]	0.52	130 [51-180]	135 [80-264]	0.65
d-dimer mg/L	1.15 [0.38-2.76]	1.58 [0.58-5.19]	0.34	0.49 [0.35-1.73]	1.01 [0.39-4.65]	0.20

troponin ng/L	7 [5-17]	7 [13-29]	0.04*	6 [5-17]	13 [8-25]	0.04*

* Statistically significant, [IQR] interquartile range with median, (SD) standard deviation with mean, interquartile range, ms milliseconds, mm millimetres, mmHg millimetre mercury, n number, TAPSE Tricuspid Annular Plane Systolic Excursion, RVSP right ventricular systolic pressure, RVS' right ventricular systolic excursion velocity, cm/s centimetre per second, RVFWS right ventricular free wall strain, RA right atrial, E E wave, A A wave, RV right ventricular, IVC inferior vena cava, LVEF left ventricular ejection fraction, CRP C reactive protein

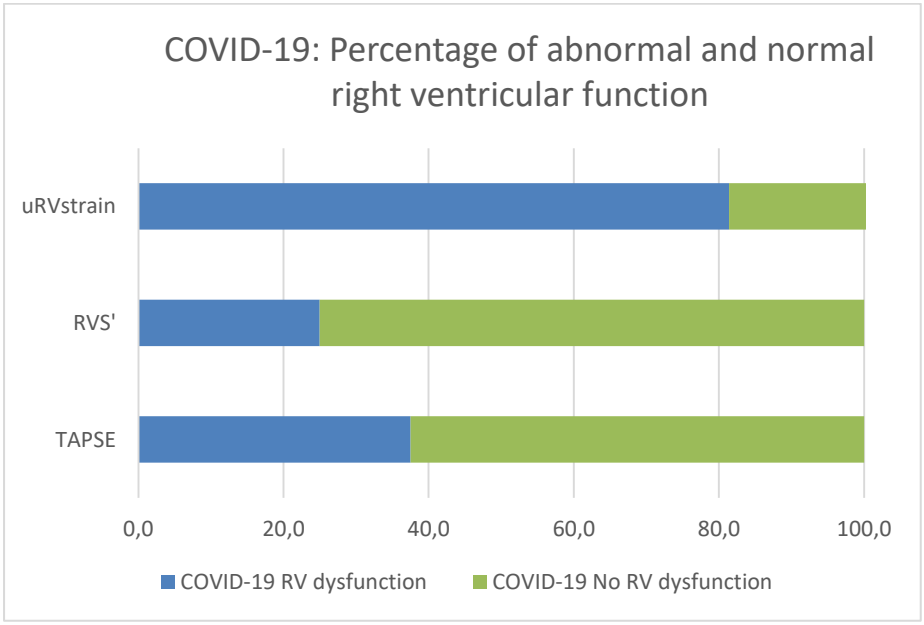

Figure 2: Prevalence of right ventricular dysfunction according to traditional echocardiographic parameters (RVS' and TAPSE) and RVFWS amongst COVID-19 patients at admission

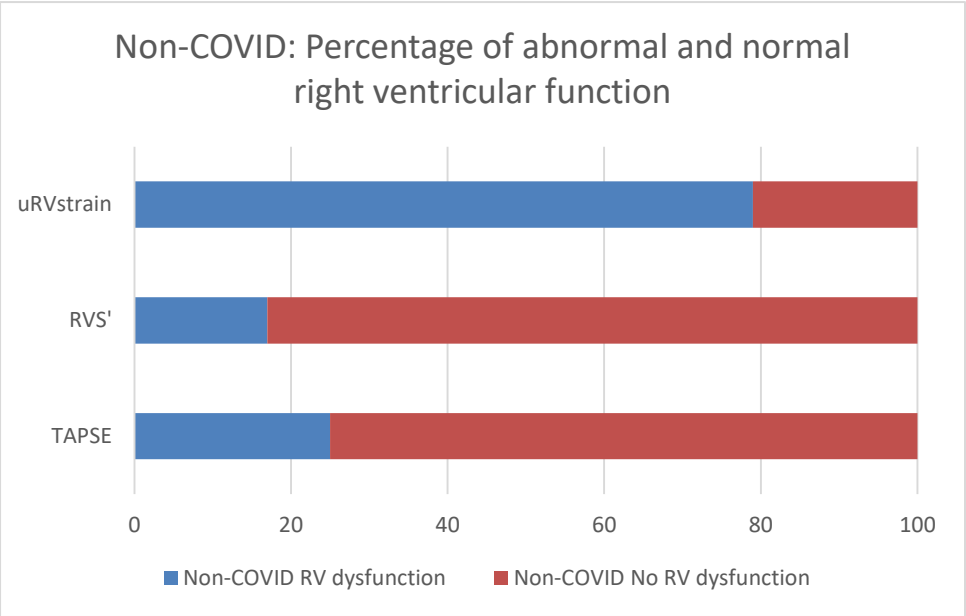

Figure 3: Prevalence of right ventricular dysfunction according to traditional echocardiographic parameters (RVS' and TAPSE) and RVFWS amongst non-COVID-19 patients at admission

Figure 4:

Figure 4: Preserved Right ventricle free wall peak systolic strain (>-23) in a young patient with non-COVID pneumonia (left) and diminished Right ventricle free wall peak systolic strain in an older patient with COVID pneumonia (<-23) (right)