Right ventricular dysfunction and pulmonary hypertension in COVID-19: a meta-analysis of prevalence and its association with clinical outcome

Type
Research paper

Keywords
outcome, prevalence, pulmonary hypertension, COVID-19, right ventricular dysfunction

Abstract
Introduction
Rapid spread of COVID-19 has caused detrimental effect globally. Involvement of ACE2 receptor has identified COVID-19 as a multi-organ disease. Preliminary studies have provided evidence that cardiac involvement, including right ventricular dysfunction (RVD) and pulmonary hypertension (PH) were found in COVID-19 cases, even in the non-advanced stage. This meta-analysis aims to analyze the prevalence of RVD and PH, and its association with COVID-19 clinical outcome.

Material and methods
A systematic data search was conducted through PubMed, MedRxiv, ProQuest, Science Direct, and Scopus databases using constructed keywords based on MeSH terms. Any outcomes regarding mortality, severity, ICU admission, and mechanical ventilation usage were analyzed using Revman v.5.4 and Stata v.16.

Results
A total of 16 eligible studies (1,728 patients) were included. Pooled prevalence of RVD in COVID-19 was 19% (95%CI: 13%-25%); and PH was 22% (95% CI: 14%-31%). RVD was associated with increased mortality (OR=2.98 [95%CI: 1.50-5.89], p=0.002), severity (OR= 3.61 [95%CI: 2.05−6.35], p<0.001), ICU admission (OR= 1.70 [95%CI: 1.12−2.56], p=0.01), and mechanical ventilation (MV) usage (OR= 1.60 [95%CI: 1.14−2.25], p=0.007). PH was also associated with increased mortality (OR=5.42 [95%CI: 2.66-11.06], p<0.001), severity (OR=5.74 [95%CI: 2.28-14.49], p<0.001), and ICU admission (OR: 12.83 [95% CI: 3.55-46.41], p<0.001).

Conclusions
RVD and PH were prevalent in COVID-19 and associated with mortality, severity, ICU admission, and MV usage in COVID-19 patients. Bedside echocardiography examination could be considered as a novel risk stratification tool in COVID-19.
Right Ventricular Dysfunction and Pulmonary Hypertension in COVID-19: A Meta-
Analysis of Prevalence and Its Association with Clinical Outcome

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Keywords: COVID-19, right ventricular dysfunction, pulmonary hypertension, prevalence, outcome.

Trial Registry: UMIN Clinical Trial Registry (UMIN000042424)

INTRODUCTION

Rapid spread of Coronavirus disease 2019 (COVID-19) from December 2019 has caused detrimental effect globally. More than 50 million people had been infected with COVID-19, causing more than 1.2 million deaths worldwide.[1] SARS-CoV-2 was identified as the culprit and utilize angiotensin-converting enzyme 2 (ACE2) receptor for host entry. ACE2 receptor is widely expressed in lungs, heart, vascular, and intestine. Hence, COVID-19 has not limited to lung disease yet a multi-organ disease. A post-mortem study of 32 patient revealed COVID-19 caused thromboembolic injuries in lung, heart, liver, kidney, and hematopoietic system.[2]

Since ACE2 is closely related to cardiovascular system, the impact of COVID-19 on this system is inevitable. Pre-existing cardiovascular disease comorbidity was associated with a higher case fatality rate and poor prognosis.[3] Previous study has provided evidence that severe cardiac dysfunction, injury, and elevation of cardiac markers were found in COVID-19 cases.[4] On the other hand, one meta-analysis demonstrated that cardiac injury in COVID-19 is associated with a higher risk of severe disease (13.81 folds), ICU admission (7.94 folds), and mortality (7.95 folds), respectively.[5]. Taken together, bidirectional interaction between COVID-19 and cardiac condition that impair cardiac and lung functions was inevitable, especially the involvement of right ventricular dysfunction and pulmonary hypertension.[6, 7]

The mechanisms behind this interaction are not yet established. Release of systemic cytokine, systemic inflammation, and pro-thrombotic state may be responsible. Furthermore,
hypoxic vasoconstriction of the pulmonary vascular in COVID-19 patients could alter pulmonary hemodynamics, damaging lungs tissue that leads to pulmonary hypertension (PH) and right ventricular dysfunction (RVD).[8, 9] One case series had described 5 cases of acute cor-pulmonale in critically ill COVID-19 patients.[10] Acute respiratory distress syndrome (ARDS) has been frequently reported among critically ill COVID-19 patients, and elevated RV afterload could also lead to RV function impairment.[11]

Preliminary pathological findings indicate alveolar septal thickening, lung edema, inflammatory infiltrates, and vascular congestion in the early stages of the disease. PH and secondary RVD may be determined by lung parenchymal disruption and altered pulmonary haemodynamics in patients with COVID-19, even in the non-advanced stage of the disease.[7]

Interestingly, early echocardiography studies regarding RVD and PH parameters in COVID-19 revealed their potential as novel risk-stratification in COVID-19 patients since it outperformed others risk factors.[12, 13] Despite its potential in COVID-19 risk-stratification, to the best of our knowledge, there is no meta-analysis that has evaluated clinical outcomes regarding RVD and PH in COVID-19. Therefore, this study aims to analyze the prevalence of RVD and PH along with their association with COVID-19 clinical outcomes.

MATERIAL AND METHODS

Study Design and Search Strategy

This systematic review and meta-analysis were performed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Initial title and abstract screening were performed in 5 online databases (PubMed, MedRxiv, ProQuest, ScienceDirect, and Scopus) using "COVID-19", "right ventricular dysfunction", "cardiac function", "pulmonary hypertension", "echocardiography", "severity", "death", "mechanical ventilation", and its synonyms as searching keywords. The search period was on November
2020. We included all studies that reported adult COVID-19 patients with any data regarding right ventricular dysfunction or pulmonary hypertension and clinical outcome. All types of criteria and definitions of RVD and PH were included in this study. Additionally, any transthoracic echocardiographic parameters for RV function and PH were also included. Studies with incomplete data and not written in English were excluded.

**Data extraction**

Three authors independently screened the relevancy of titles and abstracts after removing duplicates. Study that met inclusion criteria then assessed for full-article and further reviewed before data extraction. Subsequently, authors extracted the data, composed of authors, year of publication, study design, location, peer-reviewed publication status, sample size, male percentage, mean age, comorbidities, RVD and PH definitions, echocardiography profile, and severity criteria in each comparison group. All extracted data were collected in a dedicated Excel spreadsheet.

**Outcome**

The primary outcome in our meta-analysis was the association of RVD and PH with in-hospital mortality of COVID-19. The secondary outcome was disease severity, ICU admission, the need for mechanical ventilation. We define disease severity criteria based on World Health Organization (WHO) and National Health Commission of People's Republic of China.[14] If the study categorized severity into 3 or 4 groups, we combined the data between mild and moderate groups into one group as non-severe; severe and critical groups into one group as severe. These outcomes were classified in RVD and non-RVD or PH and non-PH. Additionally, echocardiographic parameters were also compared and classified based on each
outcomes, namely survivors and non-survivors; severe and non-severe, admitted and not admitted to ICU; used and non used mechanical ventilation.

Quality assessment and Publication bias

Two authors independently assessed study methodological quality using Newcastle-Ottawa Scale (NOS) for non-randomized studies. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used to assess the quality of the body of retrieved evidence (GRADEpro Guideline Development Tool [Software]. McMaster University, 2020). Egger's and Harbord's regression test was used to assess publication bias for continuous and binary endpoints, respectively. In addition, funnel plots was used to determine the symmetrical distribution of the effect size outcomes.

Data analysis

All analyses was performed using Revman version 5.4 and Stata v.16. We used Mantel-Haenszel formula for dichotomous variables to calculate the pooled odds ratios (ORs). Random-effect model was performed if there was heterogeneity ($I^2>50\%$). Otherwise, the fixed-effects Mantel-Haenszel model was used. The cause of heterogeneity was assessed using sensitivity analysis with leave-one-out method. We also performed the meta-analysis using a mean difference (MD) for echocardiographic parameters of RV function and PH. Mean and standard deviation were extrapolated from sample size, median, and interquartile range (IQR), according to Wan et al.[15] The average of mean and standard deviation between two groups was calculated using the formula in Table 7.7.a of the Cochrane Handbook.[16] Restricted maximum likelihood random-effects meta-regression was performed for age, sex, cardiovascular disease (CVD), hypertension (HTN), diabetes mellitus (DM), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), venous thromboembolism
(VTE), and smoking. Statistically significant was defined by p-value less than 0.05, except for heterogeneity (p<0.10).

RESULTS

Baseline characteristics and study selection

We found 584 records from the PUBMED, Science Direct, ProQuest, Scopus, and Medrxiv databases, as shown in Figure 1. Seven additional records were acquired from other sources, and 503 records remained after duplicate removal. A sum of 453 records was removed after title and abstracts screening. Fifty full texts were then assessed for eligibility, and 34 articles were excluded because of incorrect patient population (n=3); no data of RVD/PH (n=13); no outcome of interest (n=11); and irrelevant severity criteria/ group (n=4). As a result, we included 16 eligible studies (1,728 patients) for analysis.

Baseline characteristics of the included studies are presented in tables 1 and supplementary table 1. Echocardiographic parameters of included studies are described in supplementary table 2. Eleven studies were retrospective, and five studies were prospective observational. One study was published in the preprint server.[17] Most studies were conducted in China. Tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP) was used to define RVD and PH in most of the included studies, respectively. Quality Assessment and Pubication Bias

Quality of the total included studies showed good and fair methodology based on NOS assessment (supplementary table 1). However, most studies did not assess exposure before outcome measures and might not have adequate time-frames for outcome due to their cross-sectional design.

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) showed a very low certainty of evidence for effect of RVD on mortality and MV usage; and
low certainty of evidence on severity and ICU admission. While the effect of PH on mortality demonstrated high certainty of evidence and moderate certainty on severity, ICU admission, and MV usage, respectively (supplementary table 3).

Funnel plots of RVD and outcome of mortality, severity, and MV showed a qualitatively asymmetrical appearance indicating publication bias, but not for ICU outcome (supplementary figure 1). Funnel plots of PH and outcome of severity and ICU admission also showed a qualitatively asymmetrical appearance indicating publication bias, but not for mortality outcome (supplementary figure 2). Regression-based Harbord's or Egger's test were not conducted due to lack of included studies (<10 studies) in each outcome.

**Right Ventricular Dysfunction in COVID-19**

RVD and RV function echocardiography parameters data were reported in 16 studies. Most studies defined RVD by TAPSE<16-17 mm. Study by Rath et al. (2020)[19], Li et al. (2020)[11], and Krishnamoorthy et al. (2020)[21] define RVD by TAPSE<20 mm, RV free wall longitudinal strain (RVFWS) ≤ 20.5%, and RV global longitudinal strain (RVGLS) - RVFWS criteria in American Society of Echocardiography (ASE) guideline, respectively. Two studies specifically enrolled COVID-19 patients with heart transplant[18] and myocardial injury[24].

Pooled prevalence of RVD from 14 studies was 19% (95%CI: 13%–25%; I²: 90.74%, p<0.001) (figure 2A). However, analysis for PH-matched studies (6 studies) showed prevalence of RVD was 13% (95%CI: 6%–19%; I²: 83.75%, p<0.001) (figure 2B).

Mortality outcome was analyzed from 8 studies and 965 participants. Pooled analysis with random-effects showed RVD group had higher mortality rate compared to non-RVD group (OR= 2.98 [95%CI: 1.50-5.89], p=0.002; I²=67%, p=0.004) (figure 3A). A sensitivity analysis by removing study by Li et al. (2020)[11] or Liu et al. (2020)[28] exhibited consistent
result with lower heterogeneity (OR= 2.55 [95%CI: 1.27–5.13], p=0.009; $I^2$=63%, p=0.01; and

(OR= 2.51 [95%CI: 1.31–4.81], p=0.005; $I^2$=63%, p=0.01, respectively). Subsequently, when
pre-printed study was removed by sensitivity analysis, the overall outcomes still showed
significant result with lower OR (OR= 2.65 [95%CI: 1.31-5.36], p=0.007; $I^2$=67%, p=0.006).

Random-effects meta-regression analysis demonstrated that the association between
RVD and increased mortality was not significantly affected by age (p=0.065), HTN (p=0.865),
CVD (p=0.206), CKD (p=0.552), COPD (p=0.839) comorbidities, and smoking (p=0.561), but
was significantly affected by male sex (p=0.036), VTE (0.044), and DM (p=0.001)
(supplementary figure 3).

RV function echocardiographic parameters, TAPSE and RV fractional area change
(RVFAC), were evaluated in 3 studies. TAPSE were significantly lower in non-survivors group
using random-effects analysis. (MD= -3.38 [95%CI: -5.87 to -0.89] p=0.008; $I^2$=79%,
p=0.008)(figure 3B). Removing study by Liu et al.[28] exhibited same result with reduced
heterogeneity (MD= -2.16 [95%CI: -3.60 to -0.71] p=0.003; $I^2$=0%, p=0.91). Similarly,
RVFAC were lower in non-survivors group with low heterogeneity (MD= -5.75% [95%CI: -
8.23 to -3.26] p=0.001; $I^2$=0%, p=0.41)(figure 3C).

Pooled analysis of 4 studies showed more severe clinical presentation was observed in
RVD group using fixed-effect analysis (OR= 3.61 [95%CI: 2.05–6.35], p<0.001; $I^2$=0%,
p=0.53) (Supplementary figure 4A). Random-effects meta-regression analysis demonstrated
that the association between RVD and increased severity was not significantly affected by male
sex (p=0.595), age (p=0.699), HTN (p=0.741), CVD (p=0.179), and DM (p=0.925)
comorbidities.

Additionally, various echocardiographic parameters were analyzed. Evaluation of
TAPSE was performed in 3 studies with total of 220 patients and were significantly lower in
severe condition (MD= -1.30 [95%CI: -2.03 to -0.57], p=0.0005; $I^2$=0%, p=0.68)
RVGLS was evaluated in 2 studies and significantly higher in severe disease. (MD= 3.33 [95%CI: 0.85–5.82], p=0.009; I²=0%, p=0.39) (Supplementary figure 4C). Both RVFAC and RV s’ were not statistically difference in both groups (MD= -1.48% [95%CI: -4.33% to 1.36], p=0.31; I²=0%, p=0.82; and MD= -0.51 [95%CI: -1.16 to 0.14], p=0.12; I²=0%, p=0.73, respectively) (Supplementary figure 4D and 4E).

ICU admission was analyzed from a total of 311 patients from 5 studies. Overall, COVID-19 patients with RVD had higher ICU admission (OR= 1.70 [95%CI: 1.12–2.56], p=0.01; I²=0%, p=0.69) (Supplementary figure 5). However, removing study by Giustino et al.[24] demonstrated no difference between group (OR= 1.49 [95%CI: 0.88–2.535], p=0.14; I²=0%, p=0.65). Analysis of echocardiographic parameters was not performed due to limited study data.

Random-effects meta-regression analysis demonstrated that the association between RVD and ICU admission was not significantly affected by male sex (p=0.631), age (p=0.196), HTN (p=0.455), CVD (p=0.970), DM (p=0.567), CKD (p=0.938), COPD (p=0.346), and smoking (p=0.450).

Seven studies evaluated RVD and MV use. Pooled analysis using random-effects revealed higher mechanical ventilation use in RVD groups (OR= 1.60 [95%CI: 1.14–2.25], p=0.007; I²=51%, p=0.06) (Supplementary figure 6). However, after excluding study by Li et al.[11], there was no difference between groups (OR= 1.40 [95%CI: 0.97–2.01], p=0.07; I²=34%, p=0.18), indicating a lack of statistical robustness. Moreover, removing participants with heart transplant[18] and current myocardial injury[24] also showed no difference (OR= 1.33 [95%CI: 0.89–2.00], p=0.17; I²=42%, p=0.14). Analysis of echocardiographic parameters was not performed due to limited study data.

Random-effects meta-regression analysis demonstrated that the association between RVD and need for MV was not significantly affected by male sex (p=0.089), age (p=0.422),
Pulmonary Hypertension in COVID-19

Pulmonary hypertension (PH) in COVID-19 patients was reported in nine studies. Most of the studies defined PH as PASP>35-40 mmHg. A pooled analysis from six studies yielded the prevalence of PH in COVID-19 was 22% (95% CI: 14% - 31%; $I^2=83.02\%$, $p<0.001$), as shown in figure 4.

A total of 294 COVID-19 patients with PH in three studies demonstrated the mortality outcome. A pooled analysis using fixed-effect model showed that PH was significantly associated with increased risk of mortality (OR=5.42 [95%CI: 2.66-11.06], $p<0.001$; $I^2=0\%$, $p=0.77$), as shown in figure 5A. Sensitivity analysis using leave-one-out method showed no difference in heterogeneity, likewise when pre-printed study by Ge et.al [17] was removed, the overall result showed increase mortality (OR=5.75 [95%CI: 2.49-13.27], $p<0.0001$; $I^2=0\%$, $p=0.52$). Furthermore, random-effect meta-analysis of PH echocardiographic parameters found that pulmonary artery systolic pressure (PASP) was significantly higher in PH group (MD=15.23 [95%CI: 7.80-22.66], $p<0.0001$; $I^2=53\%$, $p=0.15$) (figure 5B).

Random-effects meta-regression analysis demonstrated that the association between PH and mortality was not significantly affected by male sex ($p=0.803$), age ($p=0.677$), HTN ($p=0.504$), CVD ($p=0.691$), DM ($p=0.817$), CKD ($p=0.589$), COPD ($p=0.589$), and smoking ($p=0.777$).

A pooled of 202 patients from two studies[26, 27] (were included to be analysed. As shown in supplementary figure 7, fixed-effect model yielded that PH group presented with more severe outcomes in COVID-19 patients (OR=5.74 [95%CI: 2.28-14.49], $p<0.001$; $I^2=0\%$, $p=0.37$). Interestingly, random-effect analysis revealed that the PASP between two groups was...
not significantly different (MD = 3.24 [95% CI: -1.60-8.07], p=0.19; \( \Gamma^2=73\%\), p=0.02).

Sensitivity analysis demonstrated reduced heterogeneity when Barman et al.[26] was removed from the pooled analysis (MD = 0.90 [95% CI: -1.96-3.76], p=0.54; \( \Gamma^2=0\%\), p=0.84).

ICU admission data were reported in two studies. The incidence of ICU admission was demonstrated in supplementary figure 8. Fixed-effect model showed that PH was associated with increased incidence of ICU admission (OR: 12.83 [95% CI: 3.55-46.41], p<0.001; \( \Gamma^2=0\%\), p=0.52).

**DISCUSSION**

Present result of our meta-analysis showed that both RVD and PH in COVID-19 patients were associated with increased mortality, severity, ICU admission, and MV usage. Meta-regression revealed only male sex significantly affected mortality in RVD, but not in PH. Other comorbidities such as HTN, CVD, DM, CKD, COPD, and smoking did not affect the aforementioned outcomes. It is worthy to note that the heterogeneity of our analysis for the effect estimates was moderate, and the certainty of the evidence was moderate to high in PH outcomes. Nevertheless, due to serious risk of bias in RVD outcomes, the certainty of the evidence remains low. To the best of our knowledge, our findings served the recent evidence of RVD and PH in COVID-19 patients along with its association of the various clinical outcomes in one study.

Cardiac involvement in COVID-19 is well-recognized. Interestingly, earlier studies demonstrated RV abnormalities were more common compared to LV. Study from Wuhan in early 2020 reported decreased RVFWS was found in 55.8%, while decreased left ventricle (LV) global longitudinal strain (GLS) was 34.9%. Additionally, patients with TAPSE <17mm were slightly more frequent than decreased LV ejection fraction (LVEF) findings.[28] Another study in Tel-Aviv reported 39% of hospitalized COVID-19 patients had RV dilatation or
dysfunction, while only 10% and 16% of patients had LV systolic and diastolic dysfunction, respectively.[29]

Mechanisms related to RVD in COVID-19 are unclear.[30] Numerous mechanisms are hypothetically possible in development of RV abnormalities. First, a possible mechanism is increased RV afterload. Hypercoagulability state in COVID-19 increases the occurrence of pulmonary thromboembolism and acutely increases RV afterload due to pulmonary hypoxic vasoconstriction. Besides, modulation of ACE2 by SARS-CoV-2 is also predicted to alter pulmonary hemodynamics, rising pulmonary vascular resistance.[30] Respiratory distress and MV usage in COVID-19 might also increase RV afterload, therefore contributing to RVD development.[31] Another possible mechanism is cardiac injury. Cardiac injury in COVID-19 often affects RV and spares LV.[29] Injury in RV logically explains high-sensitive troponin elevation, despite normal LV function.[12] Finally, ischemic condition from LV or vascular dysfunction possibly influences RV performance.[30]

Despite its unclear mechanism, RVD is often associated with poor clinical outcome in COVID-19. One study claimed RV echocardiographic findings provide better risk stratification over conventional risk factors. Univariable Cox-model showed RV dysfunction and RV dilatation relatively better in predicting all-cause mortality compared to other risk factors, including LV echocardiographic findings. (HR=2.57 [95%CI 1.49-4.43], p=0.001; and HR=1.43 [95%CI: 1.05-1.96], p=0.02, respectively). Additionally, combining either RV dysfunction or dilatation provides comparable hazard ratio to RV dysfunction alone (HR=2.76 [95CI%: 1.73-4.39], p<0.001).[13] Similarly, a study in England demonstrated RVD outperforming conventional risk factors, namely sex, HTN, or diabetes, in predicting all-cause of mortality (HR=1.80 [95%CI: 1.05-3.09], p=0.032). Furthermore, the same study confirmed RVD could be used universally in all races, including Black, Asian, and other minority patients. [12]
Contrary to our result, a study by Pagnesi et al. demonstrated RVD was not associated with in-hospital all-cause mortality or ICU admission (Log-rank p-value=0.464). That study explained that PH is better in evaluating COVID-19 related hemodynamic changes, specifically in non-critically ill populations, which moderate changes in pulmonary artery pressure and are inadequate to cause secondary RV dysfunction. Further, RVD might be more related to MV usage.

Our result showed RV parameters such as TAPSE, RVFAC, and RVGLS were significantly different in patients with poor clinical outcomes. This analysis confirms the study by Li et al. showing decreased TAPSE, RVFAC, and RVLS in the non-survivors group. Moreover, analysis of receiver-operating characteristic curve showed RVLS had the highest performance for poor clinical outcome, followed by RVFAC and TAPSE. Yet, the optimal cut-off values were higher than the current guideline.

SARS-CoV-2 binds to ACE2 receptors, which are highly distributed in the lung and alters its function leading to lung dysfunction, including PH. The exact pathomechanism and association of PH with poor outcomes in COVID-19 patients need to be elucidated. Of the different investigated pathways, there are several potential mechanisms of PH in COVID-19. In response to lung injury, especially due to SARS CoV-2 infection, there is an abundance of evidence showed that ACE2 receptor, as the main port of entry by the virus, is known to be down-regulated in PH. As a consequence, the concentration of angiotensin II, which contributes to lung inflammation and injury, tends to be elevated, and the protective role of ACE2 by converting angiotensin II to angiotensin (1-7) is diminished. At the same time, elevated Endothelin-1 in PH also down-regulated ACE2, inducing further vasoconstriction. Intriguingly, the hypercoagulability and inflammatory state in COVID-19 promotes the development of VTE and microthrombi that obstruct the pulmonary vessel,
leading to PH.[35] In the current cases, microvascular injury plays a key role in the development of PH in COVID-19 patients.[36]

It is well-known that COVID-19 causes multi-organ damage, and the presence of cardiac and lung injury may worsen the outcomes. Esposito et.al[37] reported that non-survivor groups in COVID-19 patients displayed an elevated PASP compared to survivor groups. This study also revealed that PH, as diagnosed by enlarged main pulmonary artery diameter, was a predictor of mortality (HR [95%CI]: 1.741 [1.253–2.418], p < 0.001), likewise, our result mortality was higher in PH groups. Moreover, the prevalence of PH in patients that develop cardiac injury is higher compare to non-cardiac injury.[26].

In fact, PH and RV dysfunction in COVID-19 is a part of vicious cycle and associated with worse conditions. An increase in pulmonary artery pressure resulted in an increase in RV afterload that may continue to RV dysfunction.[26] In addition, ARDS as a complication in COVID-19 lead to respiratory failure that needs MV application, and such MV further increase PASP and exacerbate RV dysfunction. In line with our findings, a study in Europe showed that 66.67% of patients admitted to ICU required MV, and the overall mortality rate in PH was 20%.[38] Another retrospective observational study previously reported that 63.6% of the total samples were admitted to ICU, whereas 28.57% of them underwent MV. [39] This study also reported that the mortality rate among PH patients was 36.36%, directly attributable to COVID-19. The authors revealed that systemic hypertension and diabetes mellitus were associated with severity of the disease, however, our meta-regression proved that these comorbidities were not significantly affected.

Clinical Implication and Study Limitation

This study provides evidence regarding the importance of RVD and PH in COVID-19. RVD and PH parameters could be evaluated easily by bedside transthoracic echocardiography.
These parameters could be developed as novel risk-stratification in COVID-19 patients since it outperformed conventional risk factors in previous evidence.\cite{12, 13} This study also supports experts statements and consensus on the need for point-of-care ultrasound during the pandemic, which involves the measurement of right ventricle size and function, along with pulmonary artery systolic pressure.\cite{40–42} In addition, evaluation in RVD and PH may provide a novel strategy and insights for COVID-19 managements.

Nevertheless, our study has several limitations. Publication bias was noted in several outcomes. Most of the included studies in this meta-analysis were retrospective observational, with a relatively small sample size, and were not adequately matched/adjusted for confounders. Thus, the included studies were subject to potential confounders that may weaken or strengthen the effect estimate. The result of the meta-regression has to be interpreted cautiously due to the known limitations of such analysis. Definition of RVD and PH were slightly different between studies. Definition of RVD was mostly based on TAPSE<16mm or TAPSE<17mm, while most PH was defined based on PASP>35mmHg or PASP>40mmHg. Yet, other variance in RVD and PH definition should not be neglected. Our study did not evaluate pre-existing RVD or PH, which may cause a biased result. Lastly, despite the fact that RV's structural feature is not included in our objective, structural findings may reflect chronicity of RVD or PH, therefore, may provide further information regarding its mechanism in COVID-19.

**CONCLUSION**

RVD and PH were prevalent in COVID-19 and associated with mortality, severity, ICU admission, and MV usage in COVID-19 patients. Bedside echocardiography examination could be considered as a novel risk stratification tool in COVID-19.

**References**


**Figure legends**

**Figure 1.** Study flow chart (as per PRISMA guideline)

**Figure 2.** RVD prevalence in COVID-19 patients: (A) total included studies and (B) PH-matched studies. PH: pulmonary hypertension; RVD: right ventricular dysfunction.

**Figure 3.** (A) Mortality rate in COVID-19 patients with RVD. Comparison of RV function echocardiographic parameters: (B) TAPSE and (C) RVFAC in survivors vs. non-survivors. RV: right ventricle; RVD: RV dysfunction; RVFAC: RV fractional area change; TAPSE: tricuspid annular plane systolic excursion.

**Figure 4.** PH prevalence in COVID-19 patients. PH: pulmonary hypertension.

**Figure 5.** (A) Mortality rate in COVID-19 patients with PH. (B) Comparison of PASP in survivors vs. non-survivors. PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension.
Table 1. Baseline characteristics of included studies.

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<td>2</td>
<td>Rath D, 2020[19]</td>
<td>Prospective observationa l</td>
<td>German y</td>
<td>Feb-Mar, 2020</td>
<td>123 (16 vs 107)</td>
<td>62.6 (75.0 vs 60.7)</td>
<td>68±15 (73±16 vs 67±15)</td>
<td>69.9 (75 vs 69.2)</td>
<td>CAD: 22.8 (37.5 vs 20.6); AFib: 22.8 (25 vs 22.4)</td>
<td>24.4 (31.3 vs 23.4)</td>
<td>11.4 (12.5 vs 11.2)</td>
<td>n/a</td>
<td>0.8 (0.0 vs 0.9)</td>
</tr>
<tr>
<td>3</td>
<td>Pagnesi M, 2020[7]</td>
<td>Retrospective observationa l</td>
<td>Milan, Italy</td>
<td>Mar 24 - Apr 29, 2020</td>
<td>200 (Mor:19 vs 181; ICU: 7 vs 193; MV:7 vs 193; comp 25 vs 175)</td>
<td>65.5 (n/a)</td>
<td>63.67±14.19 (n/a)</td>
<td>42.0 (n/a)</td>
<td>MI: 8.5 (n/a); HF: 3.5 (n/a)</td>
<td>18.5 (n/a)</td>
<td>7.5 (n/a)</td>
<td>5.5 (n/a)</td>
<td>20.5 (n/a)</td>
</tr>
<tr>
<td>4</td>
<td>Mahmoud Elsayed HM, 2020[20]</td>
<td>Retrospective observationa l</td>
<td>UK</td>
<td>Mar 22 - Apr 17, 2020</td>
<td>74 (Mor 28 vs 46; MV 61 vs 13)</td>
<td>78 (n/a)</td>
<td>59±13 (n/a)</td>
<td>42.0 (n/a)</td>
<td>9 (n/a)</td>
<td>36 (n/a)</td>
<td>11 (n/a)</td>
<td>14 (n/a)</td>
<td>7 (n/a)</td>
</tr>
<tr>
<td>5</td>
<td>Li Y, 2020[11]</td>
<td>Prospective observationa l</td>
<td>Tongji, China</td>
<td>Feb 12 - Mar 15, 2020</td>
<td>150 (18 vs 132)</td>
<td>48 (n/a)</td>
<td>61±14 (n/a)</td>
<td>40 (n/a)</td>
<td>9.2 (n/a)</td>
<td>11.7 (n/a)</td>
<td>14.2 (n/a)</td>
<td>5.0 (n/a)</td>
<td>5.0 (n/a)</td>
</tr>
<tr>
<td>6</td>
<td>Moody WE, 2020[12]</td>
<td>Retrospective observationa l</td>
<td>UK</td>
<td>Mar 16 - May 9, 2020</td>
<td>164 (66 vs 98)</td>
<td>78 (n/a)</td>
<td>61±13 (n/a)</td>
<td>41 (n/a)</td>
<td>13 (n/a)</td>
<td>32 (n/a)</td>
<td>12 (n/a)</td>
<td>12 (n/a)</td>
<td>13 (n/a)</td>
</tr>
<tr>
<td>7</td>
<td>Krishnamoorthy P, 2020[21]</td>
<td>Retrospective observationa l</td>
<td>New York, USA</td>
<td>n/a</td>
<td>12 (5 vs 7)</td>
<td>41.7 (60 vs 28.6)</td>
<td>48.67±25.99 (59.67±6.03 vs 45.67±29.39)</td>
<td>58.3 (60 vs 57.1)</td>
<td>16.7 (40 vs 0)</td>
<td>33.3 (40 vs 28.6)</td>
<td>16.7 (0 vs 28.6)</td>
<td>8.3 (0 vs 14.3)</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>Kim M, 2020[22]</td>
<td>Prospective-retrospective observationa l</td>
<td>South Korea</td>
<td>Feb - Apr 2020</td>
<td>40 (13 vs 27)</td>
<td>50 (53.8 vs 48.1)</td>
<td>57.55±15.88 (67.67±8.31 vs 52.67±16.44)</td>
<td>37.5 (61.5 vs 25.9)</td>
<td>0 vs 0</td>
<td>17.5 (30.8 vs 11.1)</td>
<td>2.5 (0 vs 3.7)</td>
<td>2.5 (0 vs 3.7)</td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>Zeng JH, 2020[23]</td>
<td>Retrospective</td>
<td>Shenzhen, China</td>
<td>Jan 11, 2020 - Apr 1, 2020</td>
<td>416 (35 vs 381); sample</td>
<td>47.6 (65.71 vs 45.93)</td>
<td>46.56±17.97 (63.83±6.57 vs 45±17.86)</td>
<td>14.42 (37.14 vs 12.34)</td>
<td>CAD: 3.13 (5.71 vs 2.89); Arrhythmia: 5.53 (28.57 vs 3.41)</td>
<td>0.48 (0 vs 0.52)</td>
<td>1.2 (2.86 vs 1.05)</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>
Data were presented as poor vs. good outcome.

<table>
<thead>
<tr>
<th>Study</th>
<th>Author</th>
<th>Design</th>
<th>Site</th>
<th>Dates</th>
<th>Sample Size</th>
<th>ECHO Observations</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Ge H</td>
<td>Prospective</td>
<td>Shanghai, China</td>
<td>Jan 21, 2020 - Apr 8, 2020</td>
<td>57 (31 vs 26)</td>
<td>69±16.02</td>
<td>0.96 (5.71 vs 0.52); VHD: 0.48 (2.86 vs 0.26)</td>
</tr>
<tr>
<td>11</td>
<td>Giustino G</td>
<td>Retrospective</td>
<td>New York, USA</td>
<td>Mar - May 2020</td>
<td>305 (190 vs 115)</td>
<td>63±14.9</td>
<td>37.4 (42.1 vs 29.6)</td>
</tr>
<tr>
<td>12</td>
<td>Stöbe S</td>
<td>Retrospective</td>
<td>Germany</td>
<td>Apr 2020</td>
<td>18 (14 vs 4)</td>
<td>64±19.1</td>
<td>15.6 (22 vs 8)</td>
</tr>
<tr>
<td>13</td>
<td>Barman HA</td>
<td>Retrospective</td>
<td>Istanbul, Turkey</td>
<td>Mar 25 - Apr 15, 2020</td>
<td>90 (44 vs 46)</td>
<td>56.3±19.91</td>
<td>56.7 (59 vs 55)</td>
</tr>
<tr>
<td>14</td>
<td>Kim J</td>
<td>Retrospective</td>
<td>New York, USA</td>
<td>Mar 12, 2020, and May 17, 2020</td>
<td>268 (41 vs 227)</td>
<td>66±14.13</td>
<td>24 (24 vs 22)</td>
</tr>
<tr>
<td>15</td>
<td>Deng Q</td>
<td>Retrospective</td>
<td>Wuhan, China</td>
<td>Jan 6 - Feb 20, 2020</td>
<td>112 (67 vs 45)</td>
<td>61.6±16.37</td>
<td>17 (20.9 vs 11.1); Comp: 22.6 vs 14.8</td>
</tr>
<tr>
<td>16</td>
<td>Liu Y</td>
<td>Retrospective</td>
<td>Peking, China</td>
<td>Jan 26 - Apr 15, 2020</td>
<td>43 (22 vs 21)</td>
<td>64.5±10</td>
<td>27.9 (22.7 vs 33.3)</td>
</tr>
</tbody>
</table>

2 Data were presented as poor vs. good outcome.
Abbreviations; AFib: atrial fibrillation; CAD: coronary artery disease; CHD: congenital heart disease; Comp: composite; HF: heart failure; ICU: intensive care unit; MI: myocardial infarction; Mor: Mortality; MV: mechanical ventilation; n/a: not available; Sev: severity; VHD: valvular heart disease.
SUPPLEMENTARY MATERIALS

Right Ventricular Dysfunction and Pulmonary Hypertension in COVID-19: A Meta-Analysis of Prevalence and Its Association with Clinical Outcome

SUPPLEMENTARY FIGURES

(A) RVD-mortality Funnel plot
(B) RVD-Severity Funnel plot
(C) RVD-MV Funnel plot
(D) RVD-ICU Funnel plot

Supplementary figure 1. Funnel plots indicated publication bias for RVD on (A) mortality, (B) severity, and (C) MV; but not for (D) ICU outcome. ICU: intensive care unit; MV: mechanical ventilation; RVD: right ventricular dysfunction.
Supplementary Figure 2. Funnel plots indicated publication bias for PH on (A) severity and (B) ICU; but not for (C) mortality outcome. ICU: intensive care unit; MV: mechanical ventilation; PH: pulmonary hypertension.
Supplementary figure 3. Meta-regression analysis showed that the association between RVD and increased mortality was affected by (A) male sex (B) VTE, and (C) DM. RVD: right ventricular dysfunction; VTE: venous thromboembolism; DM: diabetes mellitus.
Supplementary Figure 4. (A) Disease Severity in COVID-19 patients with RVD. Comparison of RV echocardiographic parameters: (B) TAPSE, (C) RVGLS, (D) RVFAC, and (E) RV s’ severe vs. non-severe. RV: right ventricle; RVD: RV dysfunction; RVFAC: RV fractional area change; RVGLS: RV global longitudinal strain; TAPSE: tricuspid annular plane systolic excursion.
Supplementary Figure 5. ICU Admission in COVID-19 patients with RVD. ICU: intensive care unit; RVD: RV dysfunction.

Supplementary Figure 6. Mechanical Ventilation Use in COVID-19 patients with RVD. RVD: RV dysfunction.

Supplementary Figure 7. (A) Disease Severity in COVID-19 patients with PH. (B) Comparison of PASP severe vs. non-severe. PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension.
**Supplementary Figure 8.** ICU Admission in COVID-19 patients with PH. PH: pulmonary hypertension.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PH Events</th>
<th>PH Total</th>
<th>Non-PH Events</th>
<th>Non-PH Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pagnesi M 2020</td>
<td>5</td>
<td>24</td>
<td>5</td>
<td>176</td>
<td>71.4%</td>
<td>9.00 [2.39, 33.93]</td>
</tr>
<tr>
<td>Zeng JH 2020</td>
<td>9</td>
<td>9</td>
<td>22</td>
<td>49</td>
<td>29.6%</td>
<td>22.38 [1.23, 406.20]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>33</strong></td>
<td><strong>224</strong></td>
<td><strong>9</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>12.83 [3.55, 46.41]</strong></td>
</tr>
</tbody>
</table>

Total events: 14 / 27

*Heterogeneity:* Chi² = 0.42, df = 1 (P = 0.52); I² = 0%

*Test for overall effect:* Z = 3.89 (P < 0.0001)
### Supplementary Table 1. Characteristics of RVD and PH, outcome, and quality of the included studies.

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Samples with RVD (%)</th>
<th>Samples with PH (%)</th>
<th>RVD definition</th>
<th>PH definition</th>
<th>LOS / follow up (days)*</th>
<th>Outcome</th>
<th>Severity criteria</th>
<th>Quality NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rivinius R, 2020[18]</td>
<td>28.6</td>
<td>28.6</td>
<td>n/a</td>
<td>n/a</td>
<td>follow up 60 days</td>
<td>Sev</td>
<td>Need for MV</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Rath D, 2020[19]</td>
<td>6.5</td>
<td>n/a</td>
<td>TAPSE &lt;20 mm</td>
<td>n/a</td>
<td>follow up 30 days</td>
<td>Mor</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Pagnesi M, 2020[7]</td>
<td>14.5</td>
<td>12</td>
<td>TAPSE &lt;17 mm or RV S’ &lt;9.5 cm/s</td>
<td>PASP &gt;35mm Hg</td>
<td>9±7.47 (n/a)</td>
<td>Mor, ICU, MV, comp</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Mahmoud-Elsayed HM, 2020[20]</td>
<td>27</td>
<td>16.2</td>
<td>TAPSE &lt;17 mm or RVFAC&lt;35%</td>
<td>High probability EACVI guideline</td>
<td>n/a</td>
<td>Mor, MV</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>Li Y, 2020[11]</td>
<td>33.3</td>
<td>n/a</td>
<td>RVFWS ≤20.5%</td>
<td>n/a</td>
<td>follow up 51 days</td>
<td>Mor, ICU, MV</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Moody WE, 2020[12]</td>
<td>35.4</td>
<td>16.5</td>
<td>TAPSE &lt;17 mm or RVFAC&lt;35%</td>
<td>High probability EACVI guideline</td>
<td>follow up 31 days; LoS: 25±17.2 (n/a)</td>
<td>Mor, MV</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>Krishnamoorthy P, 2020[21]</td>
<td>41.7</td>
<td>n/a</td>
<td>RVLS RVFWS ASE guideline</td>
<td>n/a</td>
<td>n/a</td>
<td>Comp Mor &amp; MV</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>Kim M, 2020[22]</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>follow up 2 months</td>
<td>Sev ATS/IDSA adults with CAP guideline 2019</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Zeng JH, 2020[23]</td>
<td>5.26</td>
<td>15.79</td>
<td>TAPSE &lt;16mm, RVFAC &lt;35%, RV S’ anterior tricuspid annulus &lt;10 cm/s</td>
<td>PASP &gt;40mmHg</td>
<td>21.95±10.0 (39.5±11.21 vs 20.33±8.19)</td>
<td>ICU</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>Ge H, 2020[17]</td>
<td>15.69</td>
<td>31.37</td>
<td>TAPSE &lt;17mm</td>
<td>PASP &gt;40mmHg</td>
<td>follow up 3 months</td>
<td>Mor</td>
<td>-</td>
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<tr>
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<td>20.81; sample with echo/myocardial injury: 35.71</td>
<td>n/a</td>
<td>TAPSE &lt;17mm; RV S’ &lt;9.5 cm/s</td>
<td>n/a</td>
<td>14.67±11.92 (n/a)</td>
<td>Mor, ICU, MV</td>
<td>Need for MV</td>
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<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Sev</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>13</td>
<td>Barman HA, 2020[26]</td>
<td>16.7</td>
<td>25.6</td>
<td>TAPSE &lt;16 mm</td>
<td>PASP &gt;35mmHg</td>
<td>10.05±4.76 (12.2±4.3 vs 8.0±4.3)</td>
<td>Sev WHO and NHC China criteria</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Kim J, 2020[13]</td>
<td>15.3</td>
<td>n/a</td>
<td>TAPSE &lt;16 mm and RV S’ 10</td>
<td>n/a</td>
<td>22.67 ± 22.03</td>
<td>Mor, ICU</td>
<td>-</td>
<td>9</td>
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<tr>
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<td>Deng Q, 2020[27]</td>
<td>3.60%</td>
<td>13.40%</td>
<td>TAPSE&lt;16mm</td>
<td>guidelines of ASE and ESC</td>
<td>n/a</td>
<td>Sev, comp mild, moderate, severe and critical types</td>
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<tr>
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<td>30.20%</td>
<td>46.50%</td>
<td>TAPSE&lt;17mm</td>
<td>PASP &gt; 40mmhg</td>
<td>n/a</td>
<td>Mor</td>
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</tbody>
</table>

*Data were presented as poor and good outcome.

Abbreviations; ICU: intensive care unit; LOS: length of stay; Mor: Mortality; MV: mechanical ventilation; n/a: not available, NOS: Newcastle Ottawa Scale; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; RVD: right ventricular dysfunction; RVFAC: right ventricular fractional area change; RVLS: right ventricular longitudinal strain; RVFWS: RV free wall longitudinal strain; RVGLS: RV global longitudinal strain; Sev: Severity; TASPE: tricuspid annular plane systolic excursion.
Supplementary table 2. Echocardiographic parameters of included studies.

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>TAPSE (mm)</th>
<th>RV S' (cm/s)</th>
<th>RVGLS (%)</th>
<th>RVFWS (%)</th>
<th>RVFAC (%)</th>
<th>PASP (mmHg)</th>
</tr>
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<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>Rath D, 2020[19]</td>
<td>Mor: 22±5 (21±6 vs 23±5)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Mor: 37±89 (30 ± 10 vs 38 ± 8.5)</td>
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<tr>
<td>3</td>
<td>Pagnesi M, 2020[7]</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>Mahmoud-Elsayed HM, 2020[20]</td>
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<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>Li Y, 2020[11]</td>
<td>Mor: 22.9±3.6 (21.0±3.3 vs 23.2±3.5)</td>
<td>Mor: 13.6±2.4 (12.9±1.9 vs 13.7±2.5)</td>
<td>n/a</td>
<td>Mor: 23.5 ±4.7 (18.5±3.1 vs 24.4±4.4)</td>
<td>Mor: 45.8 ±6.1 (41.6±6.5 vs 46.5±5.7)</td>
<td>Mor: 33.33±15.76 (47.67±12.07 vs 29.33±9.02)</td>
</tr>
<tr>
<td>6</td>
<td>Moody WE, 2020[12]</td>
<td>n/al</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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</tr>
<tr>
<td>7</td>
<td>Krishnamoorthy P, 2020[21]</td>
<td>n/a</td>
<td>n/a</td>
<td>Comp: -16.1±7.2 (-10.2±3.7 vs -20.3±6.1)</td>
<td>Comp: -16.6±8.2 (-9.8±3.8 vs -21.5±6.9)</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>8</td>
<td>Kim M, 2020[22]</td>
<td>n/a</td>
<td>n/a</td>
<td>Sev: -23.07 ±3.75 (-20.5±4.57 vs -24.3±2.66)</td>
<td>n/a</td>
<td>Sev: 47.3 ±6.67 (46.33±7.48 vs 47.77±6.34)</td>
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<td>9</td>
<td>Zeng JH, 2020[23]</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>ICU: 28.33±15.77 (34.5±19.07 vs 20.9±4.02)</td>
</tr>
<tr>
<td>10</td>
<td>Ge H, 2020[17]</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>11</td>
<td>Giustino G, 2020[24]</td>
<td>n/a</td>
<td>Sev: (12.16±4.11 vs 12.6±2.63)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Sev: 36.67±13.41 (37±14.2 vs 36±12.0)</td>
</tr>
<tr>
<td>12</td>
<td>Stöbe S, 2020[25]</td>
<td>Sev: 22±3.2 (22±3.5 vs 22±2.4)</td>
<td>n/a</td>
<td>Sev: -26.9±5.8 (-26.6±5.9 vs -27.5±6.1)</td>
<td>n/a</td>
<td>n/a</td>
<td>Sev: 26±8.7 (26±9.2 vs 26±7.8)</td>
</tr>
<tr>
<td>13</td>
<td>Barman HA, 2020[26]</td>
<td>Sev: 20.71±3.98 (20.1±4.3 vs 21.4±3.6)</td>
<td>Sev: 13.46±3.0 (13.1±3.0 vs 13.8±3.0)</td>
<td>n/a</td>
<td>n/a</td>
<td>Sev: 43.5±4.75 (41.4±4.1 vs 45.5±4.5)</td>
<td>Sev: 31.92±8.65 (35.5±8.6 vs 28.5±7.3)</td>
</tr>
<tr>
<td>14</td>
<td>Kim J, 2020[13]</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>15</td>
<td>Deng Q, 2020[27]</td>
<td>Comp: 20.0±2.3 (19.2±2.6 vs 20.3±2.2)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Data were presented as poor vs good outcome.

<table>
<thead>
<tr>
<th></th>
<th>Liu Y, 2020[28]</th>
<th>Mor: 19.0±3.7</th>
<th>(16.3±2.2 vs 21.8±2.9)</th>
<th>n/a</th>
<th>n/a</th>
<th>n/a</th>
<th>Mor: 47.2±10.9</th>
<th>(44.8 ± 10.9 vs 49.3±10.7)</th>
<th>Mor: 39.8±15.3</th>
<th>(45.1 ± 16.5 vs 34.4±12.0)</th>
</tr>
</thead>
</table>

Abbreviations, Comp: Composite; ICU: intensive care unit; Mor: Mortality; PASP: Pulmonary artery systolic pressure; RV: right ventricle; RVFAC: right ventricular fractional area change; RVFWS: RV free wall longitudinal strain; RVGLS: RV global longitudinal strain; Sev: Severity; TASPE: tricuspid annular plane systolic excursion.
Supplementary table 3. GRADE assessment of the outcomes.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect Relative (95% CI)</th>
<th>Effect Absolute (95% CI)</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Ventricular Dysfunction</td>
<td>8</td>
<td>observational studies</td>
<td>serious (^a) serious (^b) not serious not serious</td>
<td>publication bias strongly suspected strong association all plausible residual confounding would reduce the demonstrated effect (^a)^(^c)</td>
<td>89/226 (39.4%) 141/739 (19.1%)</td>
<td>222 more per 1,000 (from 70 to 391 more)</td>
<td>(\oplus)(\oplus)(\oplus)(\oplus) VERY LOW</td>
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</tr>
<tr>
<td>Mortality</td>
<td>8</td>
<td>observational studies</td>
<td>serious (^a) serious (^b) not serious not serious</td>
<td>publication bias strongly suspected strong association all plausible residual confounding would reduce the demonstrated effect (^a)^(^c)</td>
<td>70/87 (80.5%) 235/434 (54.1%)</td>
<td>269 more per 1,000 (from 166 more to 341 more)</td>
<td>(\oplus)(\oplus)(\oplus)(\oplus) LOW</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ICU admission</td>
<td>5</td>
<td>observational studies</td>
<td>serious (^a) not serious not serious not serious</td>
<td>all plausible residual confounding would reduce the demonstrated effect (^a)^(^c)</td>
<td>70/163 (42.9%) 241/672 (35.9%)</td>
<td>120 more per 1,000 (from 26 more to 230 more)</td>
<td>(\oplus)(\oplus)(\oplus)(\oplus) LOW</td>
<td></td>
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<tr>
<td>Mechanical Ventilator Usage</td>
<td>7</td>
<td>observational studies</td>
<td>serious (^a) serious (^b) not serious not serious</td>
<td>publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect (^a)^(^c)</td>
<td>125/244 (51.2%) 305/793 (38.5%)</td>
<td>115 more per 1,000 (from 31 fewer to 200 more)</td>
<td>(\oplus)(\oplus)(\oplus)(\oplus) VERY LOW</td>
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<tr>
<td>Pulmonary Hypertension</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>Study Type</td>
<td>Number of Studies</td>
<td>Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Abbreviation: CI: confidence interval; OR: odds ratio. Explanations a. Dominated by observational studies and inadequate confounding adjustments b. High heterogeneity c. Case definition varies among studies</td>
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<tr>
<td></td>
<td>observational studies</td>
<td>3</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very strong association all plausible residual confounding would reduce the demonstrated effect (^{a,c})</td>
<td>29/60 (48.3%)</td>
<td>24/234 (10.3%)</td>
<td>OR 5.42 (2.66 to 11.06)</td>
<td>280 more per 1,000 (from 131 more to 456 more)</td>
</tr>
<tr>
<td>ICU Admission</td>
<td>observational studies</td>
<td>2</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>publication bias strongly suspected very strong association all plausible residual confounding would reduce the demonstrated effect (^{a,c})</td>
<td>31/38 (81.6%)</td>
<td>80/164 (48.8%)</td>
<td>OR 5.74 (2.28 to 14.49)</td>
<td>358 more per 1,000 (from 197 more to 445 more)</td>
</tr>
<tr>
<td></td>
<td>observational studies</td>
<td>2</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>publication bias strongly suspected very strong association all plausible residual confounding would reduce the demonstrated effect (^{a,c})</td>
<td>14/33 (42.4%)</td>
<td>27/224 (12.1%)</td>
<td>OR 12.83 (3.55 to 46.41)</td>
<td>517 more per 1,000 (from 207 more to 744 more)</td>
</tr>
</tbody>
</table>
Figure 1. Study flow chart (as per PRISMA guideline)
Figure 2. RVD prevalence in COVID-19 patients: (A) total included studies and (B) PH-matched studies. PH: pulmonary hypertension; RVD: right ventricular dysfunction.
Figure 3. (A) Mortality rate in COVID-19 patients with RVD. Comparison of RV function echocardiographic parameters: (B) TAPSE and (C) RVFAC in survivors vs. non-survivors. RV: right ventricle; RVD: RV dysfunction; RVFAC: RV fractional area change; TAPSE: tricuspid annular plane systolic excursion.
Figure 4. PH prevalence in COVID-19 patients. PH: pulmonary hypertension.
Figure 5. (A) Mortality rate in COVID-19 patients with PH. (B) Comparison of PASP in survivors vs. non-survivors. PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension.