



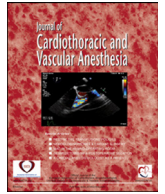
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Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Review Article

Right Ventricular Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis

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Objective: This systematic review and meta-analysis aimed to describe the features of right ventricular impairment and pulmonary hypertension in coronavirus disease (COVID-19) and assess their effect on mortality.

Design: The authors carried out a systematic review and meta-analysis of observational studies.

Setting: The authors performed a search through PubMed, the International Clinical Trials Registry Platform, and the Cochrane Library for studies reporting right ventricular dysfunction in patients with COVID-19 and outcomes.

Participants: The search yielded nine studies in which the appropriate data were available. **Interventions:** Pooled odds ratios were calculated according to the random-effects model.

Measurements and Main Results: Overall, 1,450 patients were analyzed, and half of them were invasively ventilated. Primary outcome was mortality at the longest follow-up available. Mortality was 48.5% versus 24.7% in patients with or without right ventricular impairment (n = 7; OR = 3.10; 95% confidence interval [CI] 1.72-5.58; p = 0.0002), 56.3% versus 30.6% in patients with or without right ventricular dilatation (n = 6; OR = 2.43; 95% CI 1.41-4.18; p = 0.001), and 52.9% versus 14.8% in patients with or without pulmonary hypertension (n = 3; OR = 5.75; 95% CI 2.67-12.38; p < 0.001).

Conclusion: Mortality in patients with COVID-19 requiring respiratory support and with a diagnosis of right ventricular dysfunction, dilatation, or pulmonary hypertension is high. Future studies should highlight the mechanisms of right ventricular derangement in COVID-19, and early detection of right ventricular impairment using ultrasound might be important to individualize therapies and improve outcomes.

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Key Words: right ventricle; meta-analysis; COVID-19; ARDS; echocardiography; critical care

IN DECEMBER 2019, an outbreak of pneumonia emerged in Wuhan (Hubei Province, China) and quickly was discovered

to be caused by a new coronavirus, later called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes coronavirus disease (COVID-19). Since then, the virus has spread rapidly to other provinces in mainland China and, so far, more than 200 countries. It was recognized as a

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pandemic by the World Health Organization (WHO) in March 2020.^{1,2}

The main clinical feature of the infection involves the respiratory system, further declining respiratory insufficiency with the need for supportive therapy with high-flow oxygen or non-invasive mechanical ventilation. Eventually, acute respiratory distress syndrome (ARDS) can develop, requiring invasive ventilation, prone positioning, and, in severe cases, venovenous extracorporeal oxygenation (VV-ECMO).³

Respiratory failure in patients with COVID-19 presents as a combination of two processes: viral pneumonia and ARDS. These conditions can cause diffuse alveolar damage with hyaline membrane formation followed by interstitial widening, edema, and fibrosis due to inflammation and proliferative disease.⁴

Another finding in COVID-19–related ARDS is pulmonary thrombosis that might involve pulmonary microvessels, suggesting thrombotic microangiopathy and causing pulmonary hypertension (PH), which likely increase mortality.^{5,6} This disorder could explain unexpected manifestations such as dilated pulmonary vessels and right ventricular dysfunction.⁷ In patients with COVID-19–related ARDS, pulmonary hypertension also might be due to the involvement of angiotensin converting enzyme (ACE) 2 receptors and the effects of chemokines and cytokines.⁸ Notably, cardiac failure, in particular right ventricle (RV) dysfunction, commonly is encountered in moderate-to-severe non-COVID-19 ARDS and is reported to be one of the major determinants of mortality.⁹

The aim of this systematic review and meta-analysis was to determine if echocardiographic evidence of RV dysfunction, echocardiographic evidence of RV dilation, and/or pulmonary hypertension are associated with mortality in patients with COVID-19.

Methods

The authors adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses¹⁰ to conduct and report this systematic review. The protocol was registered to the PROSPERO database with ID CRD42020216221.

Literature Search, Study Selection, and Outcomes

The authors performed a thorough literature search in PubMed, Cochrane Library, and the International Clinical Trials Registry Platform databases through October 23, 2020 to identify published or ongoing studies on the subject. The keywords used were (“COVID-19” OR “SARS-CoV-2” OR “Coronavirus”) AND (“right ventricle” OR “right heart” OR “echocardiography” OR “pulmonary hypertension” OR “pulmonary pressure”). The authors manually recorded the reference list of all significant publications. Inclusion criteria were as follows: all types of studies, studies investigating right ventricular function or pulmonary pressure assessment using echocardiography, studies in adult patients with COVID-19, and studies reporting mortality data. The authors excluded studies involving patients <18 years old, case reports or case

series, and narrative or systematic reviews. Titles and abstracts subsequently were screened by two reviewers (G.P. and P.B.) to recognize possibly relevant articles. Discrepancy in judgment was resolved after discussion. The retrieved full manuscripts were reviewed for relevancy and presence of outcomes of interest, and the list of studies to be included in the quantitative analysis was generated.

Data Synthesis and Statistical Analysis

The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized controlled trials. The methodologic power of observational studies was evaluated by the Newcastle–Ottawa Scale (NOS).¹¹ The NOS was designed to judge a study from three perspectives: the study’s selection, the comparability, and the determination of outcomes. Favorable judgment was made by awarding a star. Nine stars indicated the highest strength, and six or more stars designated elevated quality.

A meta-analysis was performed when outcomes were reported in at least two studies. Odds ratios (ORs) and 95% confidence intervals were estimated. Metric I^2 was used to assess heterogeneity among studies independently of the number of studies.¹² The random-effects model was used to calculate OR. Two-tailed p values with $p < 0.05$ were judged as statistically significant. Publication bias was assessed by visually inspecting the funnel plot when more than ten studies were found. Funnel plot asymmetry was detected using Egger’s regression test.¹³ All data from the included studies were extracted into the Review Manager (RevMan) software, version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) for macOS.

RV dysfunction was assessed by at least one or a combination of the following: fractional area change (FAC) < 35%, tissue Doppler-derived imaging (TDI) tricuspid lateral annular systolic velocity wave (S') < 9.5 cm/s, tricuspid annular plane systolic excursion (TAPSE) < 17 mm, and RV index of myocardial performance (RIMP) by TDI > 0.43, as recommended by the guidelines.¹⁴ A diameter >41 mm at the base and >35 mm at the midlevel in the RV-focused view were used to identify RV dilatation.¹⁴ PH was diagnosed by mean pulmonary arterial pressure (PAPm) > 25 mmHg, as recommended in the guidelines.¹⁵

Results

Search Results

A list of 312 studies was identified through the literature search, among which 60 were duplicates, and 200 were excluded after an initial review of titles and abstracts. The remaining 28 full-text publications were reviewed and screened for inclusion criteria (Supplement Table 1). Finally, nine were selected for systematic review and meta-analysis.^{16–24} The search and selection process is depicted in the Preferred Reporting Items for Systematic Review and Meta-Analyses flow diagram in [Figure 1](#).

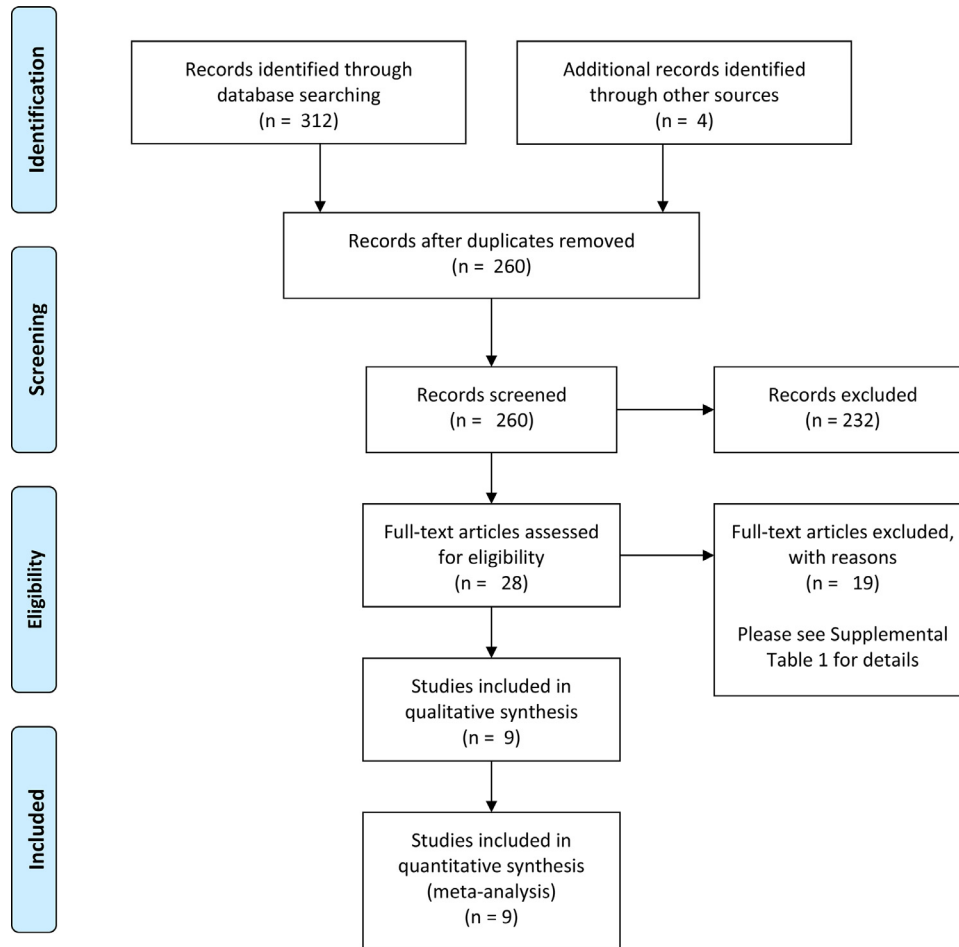


Fig 1. Preferred Reporting Items for Systematic Review and Meta-Analyses flow diagram.

Study and Patient Characteristics

Approximately half of the patients were invasively ventilated. Study details and patient characteristics are reported in Table 1 and Table 2. The nine studies included in the analysis were all observational investigations conducted in 2020.

Of the selected studies, seven evaluated the influence of RV dysfunction on mortality and included 866 patients. There was a significant increase in mortality in patients with RV dysfunction when compared with patients without RV dysfunction (121/215 [48.5%] v 199/651 [24.7%]; number of studies = seven; OR = 3.10; 95% CI 1.72-5.58; p for effect = 0.0002; p for heterogeneity = 0.001; I² = 63.0%).

Of the selected studies, six evaluated the influence of RV dilatation on mortality and included 1,102 patients. There was a significant increase in mortality in patients with RV dilatation when compared with patients without RV dysfunction (145/299 [56.3%] v 198/803 [30.6%]; n = 6; OR = 2.43; 95% CI 1.41-4.18; p for effect = 0.001; p for heterogeneity = 0.005; I² = 55.0%).

Only three studies reported data on PH for a total of 446 patients. Mortality was 72 of 136 (52.9%) versus 46 of 310 (14.8%) in patients with and without PH (n = 3; OR = 5.75; 95% CI 2.67-12.38; p for effect < 0.001; p for

Table 1
Study Characteristics

Author	Region	Study Design	No. of patients
Argulian E. 2020	USA	Retrospective	137
Garcia-Cruz E. 2020	Mexico	Multicenter, Cross-sectional, Observational	82
Jain S.S. 2020	USA	Retrospective, Observational	72
Kim J. 2020	USA	Multicenter, Retrospective, Observational	510
Li Y. 2020	China	Prospective, Observational	120
Mahmoud-Elsayed H. 2020	UK	Retrospective, Observational, Cohort	74
Moody W. 2020	UK	Multicenter, Retrospective, Observational	164
Pagnesi M. 2020	Italy	Single Center, Observational, Cross-sectional	200
Rath D. 2020	Germany	Prospective, Observational	123

Table 2
Patient Characteristics

Author	Age, y	Male	ICU	NIV	MV	RV Dilatation	RV Impairment	Mortality
Argulian E.	66 ± 14.6	58.1%	NA	NA	NA	31.0%	NA	20.0%
Garcia-Cruz E.	56 (50-66)	62.2%	NA	NA	79.0%	28.0%	46.0%	40.7%
Jain S.S.	61 (50.8-70.3)	72.2%	NA	NA	55.6%	15.3%	51.7%	33.3%
Kim J.	64 ± 14	65.5%	67.6%	43.0%	60.3%	33.6%	8.0%	31.9%
Li Y.	61 ± 14	47.5%	21%	5%	12.5%	NA	35.0%	15.0%
Mahmoud-Elsayed H.	59 ± 13	78.4%	NA	NA	78.3%	41.0%	27.0%	37.8%
Moody W.	61 ± 13	77.4%	NA	NA	73.1%	38.0%	35.3%	37.0%
Pagnesi M.	62 (55-74)	65.5%	3.5%	NA	3.5%	14.5%	NA	12.5%
Rath D.	68 ± 15	62.6%	45.5%	NA	39.8%	48.9%	13.7%	13.0%

Abbreviations: ICU, intensive care unit; MV: mechanical ventilation; NIV, noninvasive ventilation; NA: not available; RV: right ventricle; Age is indicated as mean and SD or as median and IQR (numbers in parentheses).

heterogeneity = 0.18; $I^2 = 41\%$). Forest plots of the pooled results are shown in Figure 2 (panels A-C).

Risk of Bias in Included Studies

The nine included studies were of high quality according to the NOS assessment tool for cohort studies, and the risk of bias was evaluated as detailed in Supplemental Table 2.

Discussion

To the authors' knowledge, this was the first systematic review and meta-analysis assessing the effects of RV

dysfunction or dilatation in adult patients with COVID-19. The authors found a significantly increased mortality in patients with RV dysfunction and in those with RV dilatation and/or PH compared to other patients with COVID-19 without acute right ventricular alterations.

RV dysfunction in patients with ARDS is a well-known finding; however, the authors decided to perform the present meta-analysis after increasing evidence of a strong relationship between RV failure and mortality in patients with COVID-19 patients was suggested in several studies.²⁵⁻²⁸

In the present meta-analysis, the authors included nine observational studies, which met the inclusion criteria, to evaluate the impact of right ventricular alteration on outcome in

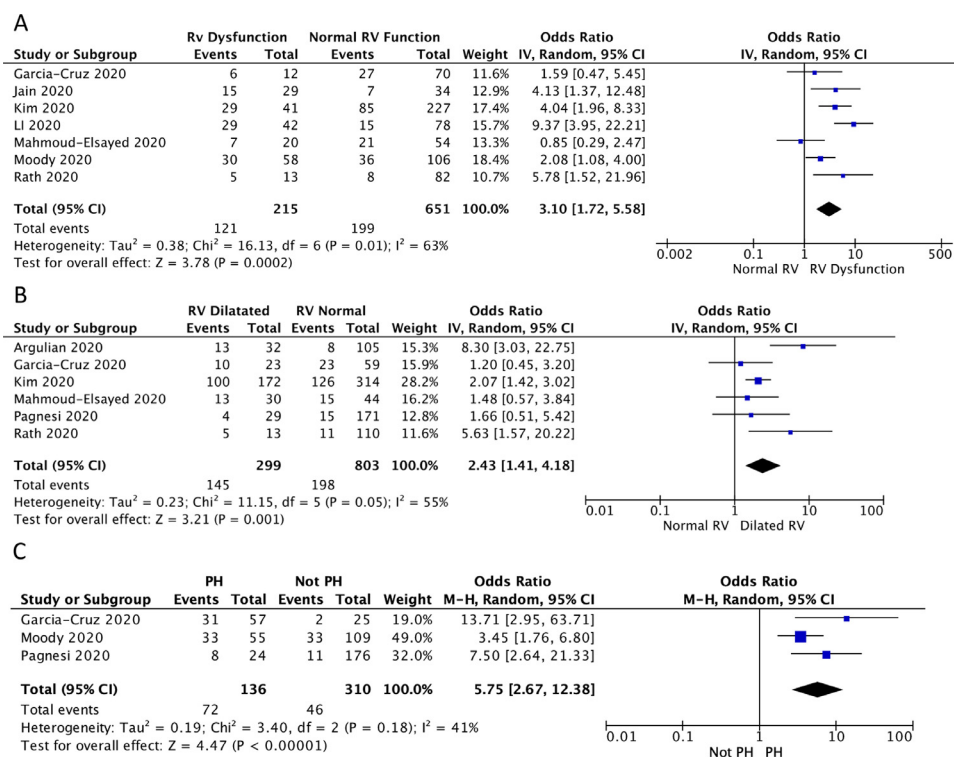


Fig 2. (A) Forest plot depicting analysis of the odds of mortality from acute respiratory distress syndrome (ARDS) in patients with coronavirus disease (COVID-19) with right ventricular dilatation. (B) Forest plot depicting analysis of the odds of mortality from ARDS in patients with COVID-19 with right ventricular dysfunction. (C) Forest plot depicting analysis of the odds of mortality from ARDS in patients with COVID-19 with pulmonary hypertension. PH, pulmonary hypertension.

patients with COVID-19. A recent survey on cardiac involvement in COVID-19 showed that the left ventricle was affected in 32% of patients, right ventricle in 42%, and both sides were involved in 21% of patients. Interestingly, only in 5% of patients was no cardiac involvement reported.²⁹ Heart failure, particularly RV dysfunction, commonly is encountered in moderate-to-severe ARDS and is reported to be one significant determinant of mortality.³⁰

The negative influence of high-pressure mechanical ventilation on hemodynamics has been recognized,³¹ as the inevitable rise in intrathoracic pressure caused by positive-pressure ventilation, or positive end-expiratory pressure (PEEP), is associated with a decrease in CO, probably mediated by impairment of venous return.³²

RV dilatation, in response to an increase in afterload, raises the right ventricular distending pressure, which can reduce the pressure gradient for the subendocardial coronary blood flow with a corresponding reduction in right ventricular contractility.³³

Along with alveolar damage, ARDS directly causes injury to the pulmonary circulation through several pathophysiologic mechanisms: hypoxic pulmonary vasoconstriction, release of vasoconstrictive mediators, extrinsic vascular compression by interstitial edema, and blood vessel remodeling. All of these factors contribute to PH, elevated pulmonary vascular resistance, increased right ventricular afterload and, eventually, RV failure. RV dysfunction is a common and often primary cause of cardiovascular insufficiency in the critically ill.³⁴

The pulmonary vascular bed is more sensitive to the vasoconstrictive influence of respiratory acidosis. Moreover, pulmonary vascular dysfunction might be associated with ARDS, leading to increased right ventricular afterload and, eventually, RV dysfunction.

In patients with COVID-19, a cytokine storm is common. Interleukin 6 (IL-6) serum concentration correlates with respiratory dysfunction, ARDS, and poor clinical outcomes. In addition, SARS-CoV-2 direct injury to the RV is expected to increase the release of vasoactive peptides and promote myocardial recruitment of inflammatory cells. Cardiac myofibroblasts and cardiomyocytes act as key sources for a wide array of pro-inflammatory cytokines, including IL-6, and are highly responsive to IL-6, IL-1 β , and TNF α . Furthermore, prolonged/excessive synthesis of IL-6 is reported to induce cardiac hypertrophy, fibrosis, and diastolic dysfunction. The proinflammatory cytokine cascade can contribute to RV dysfunction through negative inotropic effects on the myocardium. Taken together, depressed RV contractility may prove to be fatal in the face of acutely elevated pulmonary vascular resistance from ARDS and pulmonary embolism in COVID-19.³⁵

As demonstrated by this meta-analysis, the impact of right ventricle dysfunction on COVID-19 mortality highlighted the importance of echocardiographic screening in such patients throughout the clinical course, even if protective or noninvasive ventilation approaches are used.³⁶

Study Limitations

All studies included in the present meta-analysis were observational. In addition, clinical setting and ventilation protocols varied in different studies, and this should be considered. Moreover, echocardiographic RV assessment might not be homogeneous across the studies included in the meta-analysis.

Conclusions

Alterations in RV function or PH dimensions in patients with COVID-19 undergoing respiratory support seem to play a major role in determining mortality rate. Thrombotic events, hypoxemic vasoconstriction, cytokine release, and direct viral damage all are possible contributors to RV derangement. The present analysis reinforced the need for a broader implementation of screening patients with COVID-19 for right-heart alterations, and a focused ultrasound assessment might be important in patients presenting with COVID-19 needing respiratory support.

Acknowledgements

We thank Dr. Daniel Manzur Sandoval and Dr. William Moody and their colleagues for sharing their data.

Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1053/j.jvca.2021.04.008](https://doi.org/10.1053/j.jvca.2021.04.008).

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