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Review

Right ventricular-pulmonary arterial coupling in patients with COVID-19: A systematic review and meta-analysis

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Abstract

Objectives: **In this systematic review and meta-analysis, we assessed the association between right ventricular-pulmonary arterial (RV-PA) coupling and mortality in coronavirus disease 2019 (COVID-19).**
Methods: **We performed a systematic literature search using MEDLINE (PubMed), Embase, Cochrane and Web of Science. We only included observational studies and randomized controlled trials in which, right ventricular function and pulmonary pressures were investigated, in adult patients with COVID-19. The primary outcome was mortality. The secondary outcome was pulmonary embolism (PE). Random-effects meta-analysis was performed. Mean differences (MD) and unadjusted hazard ratios (HRs) were pooled.**
Results: **21 studies were included in our systematic review for qualitative analysis, and eight of them qualified for quantitative analysis. Tricuspid annular plane systolic excursion (TAPSE) over pulmonary artery systolic pressure (PASP) (TAPSE/PASP) ratio was significantly lower in non-survivors compared with survivors (mean difference = – 0.28 [–0.38, –0.17], p < 0.00001; I2: 61%, p < 0.08). TAPSE was significantly lower in non-survivors compared with survivors (mean difference = – 3.53 [–4.72, –2.33], p < 0.00001; I2: 77%, p < 0.0005). Lower TAPSE was associated with increased mortality (HR = 0.77 [0.63, 0.94], p < 0.010; I2: 77%, p = 0.01). PASP was significantly higher in non-survivors compared with survivors (mean difference = 9.14 [6.67, 11.61], p < 0.00001; I2: 37%, p=0.18). One study demonstrated a higher risk of mortality for lower TAPSE/PASP in both intensive care unit (ICU) and non-ICU patients and, one study showed that TAPSE/PASP was significantly associated with a higher risk of PE.**
Conclusion: **COVID-19 non-survivors have a significantly worse RV-PA coupling as compared to survivors.**

Keywords: **COVID-19, Ventricular Dysfunction, Right, Hypertension, Pulmonary, Echocardiography, Pulmonary artery.**

Introduction

Coronavirus disease 19 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), is an international public health issue 1. The clinical spectrum of COVID-19 is broad, ranging from mild asymptomatic disease to acute respiratory distress syndrome (ARDS) and multiorgan failure[2,3]. While COVID-19 is primarily characterized as a disease of the respiratory tract system, increasing evidence suggests that COVID-19 is a complex multisystem disorder with extrapulmonary manifestations 4. The cardiovascular system plays a crucial role in disease progression and outcome[5]. A significant proportion of COVID-19 patients develop cardiac complications including myocarditis, takotsubo cardiomyopathy, myocardial injury, arrhythmias, thrombembolism and heart failure[4,6].

The right ventricle (RV) seems to be particularly affected by COVID-19[7]. Previous research has demonstrated that RV dysfunction and increased RV afterload occur in up to one third of COVID-19 cases[2,8,9]. RV dysfunction has multiple causes

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that includes pulmonary endothelial injury, microvascular thrombosis of pulmonary vessels and hypoxic pulmonary vasoconstriction, all leading to pulmonary hypertension (PH) and hence an increase in RV afterload[2,3,10]. Invasive mechanical ventilation is often necessary for severe COVID-19, which may be another contributor to RV dysfunction, especially when high transpulmonary pressures are required to maintain normoxia and normocapnia[3]. This might result in overexpansion of the alveoli and compression of the alveolar capillaries, increasing the pulmonary vascular resistance[2,3]. Once PH is developing, the RV initially responds to the increase in RV afterload by increasing its contractility, i.e. homeometric autoregulation[11]. This mechanism allows to maintain the physiological coupling between RV contractility and RV afterload [i.e., right ventricular-pulmonary artery (RV-PA) coupling[12]]. However with further worsening of PH, the contractility of the RV will eventually decrease[11] so that RV-PA uncoupling will occur.

The standard method for the evaluation of RV-PA coupling is the measurement of the RV End-systolic elastance/Arterial elastance (Ees/Ea) ratio using intraventricular conductance catheters[13]. However, this approach is invasive, technically demanding, and unpractical at bedside[13]. RV-PA coupling can also be estimated using surrogates of Ees/Ea, of which the ratio of the tricuspid annular plane systolic excursion (TAPSE) over pulmonary artery systolic pressure (PASP) (TAPSE/PASP) is increasingly used in clinical research. The TAPSE/PASP ratio can be non-invasively assessed at bedside using transthoracic echocardiography[13].

In ARDS, pulmonary arterial hypertension (PAH) and heart failure, RV-PA uncoupling as assessed by the TAPSE/PASP ratio has been demonstrated to be an independent predictor of mortality and morbidity[13,14]. The unique pathophysiological mechanisms underlying COVID-19-associated ARDS may differ from other causes of ARDS, such as sepsis or pneumonia[15,16]. Understanding RV-PA coupling in COVID-19 patients could provide insights into the specific cardiac and pulmonary interactions that occur in this disease and give valuable prognostic information. We hypothesized that also in patients suffering from COVID-19, a decrease in the TAPSE/PASP ratio would be associated with worse outcomes. To test our hypothesis, we performed a systematic review and meta-analysis of the association between RV-PA coupling and morbidity and mortality in COVID-19.

Methods

Protocol registration

We registered the review protocol in PROSPERO (CRD42022326246). We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17,18].

Eligibility criteria

We included all studies that met each of the following criteria: 1) observational studies or randomized controlled trials in COVID-19 patients, 2) data on pulmonary pressures and right ventricular function are provided, and 3) outcome reported. The main outcome was mortality. The secondary outcomes were ICU admission, pulmonary embolism, ICU length of stay, duration of mechanical ventilation and morbidity. Articles from onset of the databases until June 1, 2022 could be included.

Excluded were review articles, commentaries, case reports, case series, letters, conference abstracts and languages other than English, French, Dutch or German[18].

Search strategy

We performed a systematic literature search using MEDLINE (PubMed), Embase, Cochrane and Web of Science. In addition, ClinicalTrials.gov and the World health organization international clinical trials registry platform search portal (ICTRP) were searched for 'grey' literature and to identify possible publication bias. We used a search string compromising two concepts: COVID-19 and RV-PA coupling (Supplementary material). We collaborated with an expert biomedical librarian to include appropriate mesh-terms and synonyms for each concept. Furthermore, we checked the reference lists of the included studies and previous systematic reviews. We also used the PICO strategy for ClinicalTrials.gov and ICTRP. There were no restrictions on the date of publication.

Study selection

The search results were screened on titles/abstracts after removing the duplicates. The full texts of the remaining studies were screened based on the inclusion and exclusion criteria. The screening process was done independently by one author. A second author was consulted at each step until an agreement was formed. The selection process was put in a PRISMA flow diagram.

Data extraction

A standardised table was used for the data extraction. Extracted items included: 1) first author, 2) year of publication, 3) study design, 4) age, 5) sex, 6)

ICU admission, 7) respiratory support measures, 8) tricuspid annular plane systolic excursion (TAPSE), 9) pulmonary artery systolic pressure (PASP), 10) RV-PA coupling and 11) mortality.

Data synthesis

TAPSE, PASP and TAPSE/PASP between non-survivors and survivors were analysed in separate meta-analyses. Studies were only included in meta-analysis when quantitative data could be extracted for one or more of these parameters[18]. When only the median value of TAPSE/PASP ratio was reported, the value was converted to the estimated mean and corresponding standard deviation using the algebraic approach proposed by Wan et al[19]. The mean differences in continuous variables were calculated with their 95% confidence intervals (CIs)[9]. The unadjusted hazard ratios were pooled with their 95% CIs. The random effects model was applied on the meta-analysis to combine mean differences and HRs[20]. Heterogeneity among studies was quantified with the χ^2 test (p-value <0, 1) and I^2 statistics (>75%). We considered $p < 0.05$ as statistically significant. Data was portrayed graphically using forest plots. All statistical analyses were performed using Review Manager (Version 5.4. The Cochrane Collaboration, September 2020).

Outcome

The primary outcome was mortality. The secondary outcomes were the effect of RV-PA coupling on ICU admission, pulmonary embolism, ICU length of stay and duration of mechanical ventilation.

Risk of Bias

To assess the risk of bias, the Newcastle-Ottawa scale was used for non-randomized controlled trials. The studies were graded using a star system based on three major criteria: the selection of the study groups; the comparability of the cohorts; and the attribution of the outcome[21].

Results

Search results

The PRISMA flow diagram illustrates the systematic search procedure (Figure 1). The systematic search yielded 3037 studies. After deduplication, 1886 studies remained. These articles were screened on titles, 93 abstracts were read, and 29 articles were selected for full-text reading. Eight studies were excluded because they did not meet one of our pre-defined eligibility criteria or because there was no full text published. 21 studies were included in our systematic review for qualitative analysis and eight of them qualified for quantitative analysis[3,14,22-40]. For the comparison of TAPSE/PASP between survivors and non-survivors, 3 studies were selected[3,14,35]. For the comparison of TAPSE between survivors and non-survivors, 6 studies were selected[14,23, 28,31,35,38]. For the comparison of PASP between survivors and non-survivors, 5 studies were selected[14,23,28,34,35].

RV-PA coupling and mortality

The TAPSE/PASP ratio of COVID-19 patients was only reported in four studies, comprising a total of 708 patients[3,14,35,37]. Both TAPSE and PASP were measured by echocardiography. In all four studies the TAPSE/PASP ratio was associated with an increased risk of mortality (Table I). Only the results of three studies could be pooled[3,14,35]. The fourth study reported its data in median ± IQR and in groups of terciles and the original data could not be retrieved[37]. This study divided its patients into groups of terciles and patients in the lowest TAPSE/PASP terciles emerged as the group that was identified as having the highest risk of death during hospitalization (Table I)[37]. Another study used the RV fractional area change/RV systolic pressure ratio (RV FAC/RVSP) in preference to TAPSE/PASP to determine RV-PA coupling in its cohort of 90 patients[39]. "Using a standard cut off for normal function of 1.0 this measure identified 85.9% (95% CI 75.4–92.4%) of patients as having RV-PA uncoupling (n = 64)"[39].

The pooled studies showed that the TAPSE/PASP ratio was significantly lower in non-survivors compared with survivors (mean difference = –0.28 [–0.38, –0.17], $p < 0.00001$; I2: 61%, $p < 0.08$) [Figure 2.]. A random-effect model was used because of the considerable heterogeneity (I2=61%).

RV function, RV afterload and mortality

14 studies examined the relationship between RV function, RV afterload and patient mortality. Both the RV function and RV afterload were measured by echocardiography. In nine studies reduced RV function or RV dysfunction and elevated RV afterload were both independently associated with mortality[3,14,24,25,31,35-37]. One study found that pulmonary hypertension and the presence of slightly, moderately, or severely impaired RV systolic function were all significantly associated with an increased mortality risk (Table I)[24]. In the second study, right ventricular dysfunction that was present at the time of admission or that was discovered at any point during ICU-stay and elevated pulmonary artery pressure were each linked to a higher risk of death after 30 days (Table I)[25]. In the third study, reduced TAPSE, increased PASP, and right ventricular diastolic dysfunction were found to be characteristics associated with in-hospital

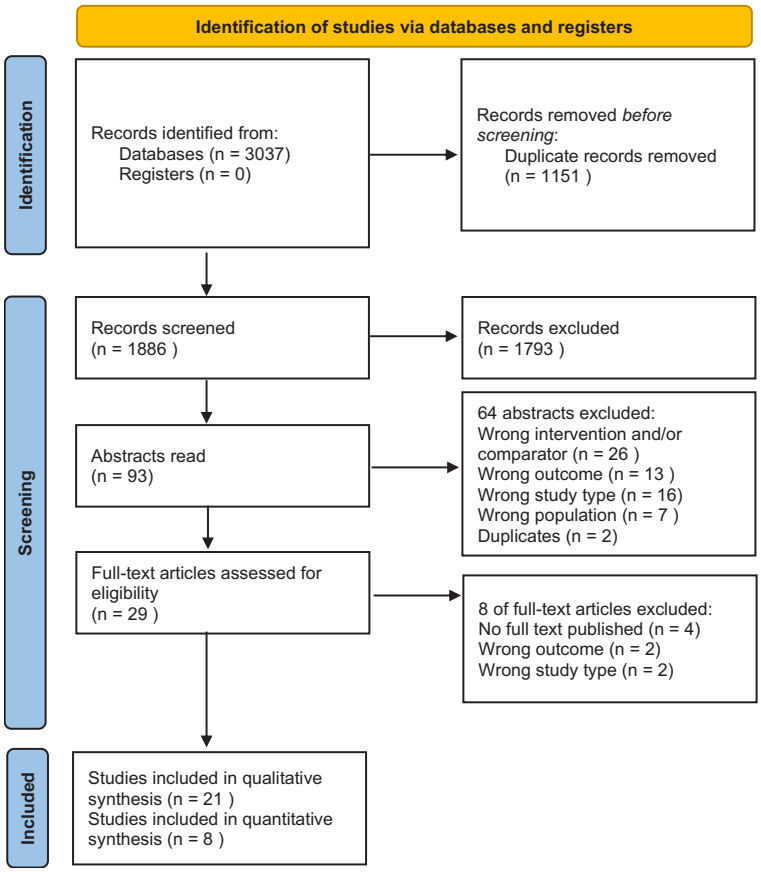

Fig. 1 — PRISMA flow chart.

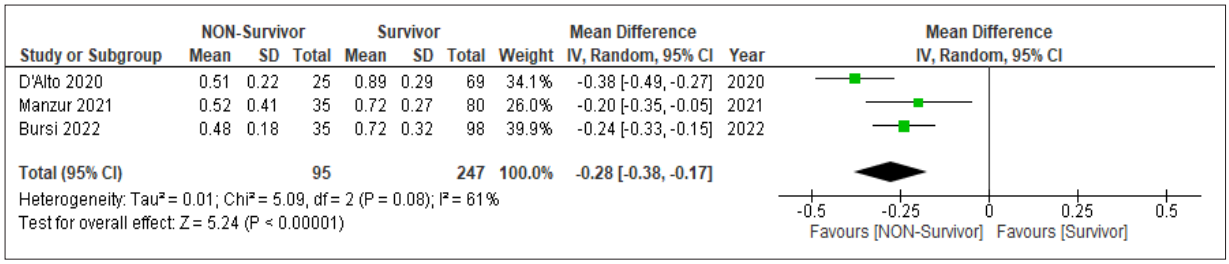

Fig. 2 — Mean difference in TAPSE/PASP between non-survivors and survivors.

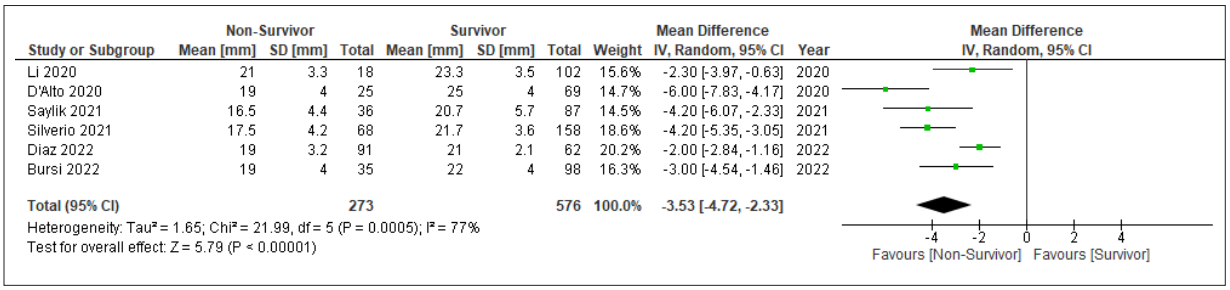

Fig. 3 — Mean difference in TAPSE between non-survivors and survivors.

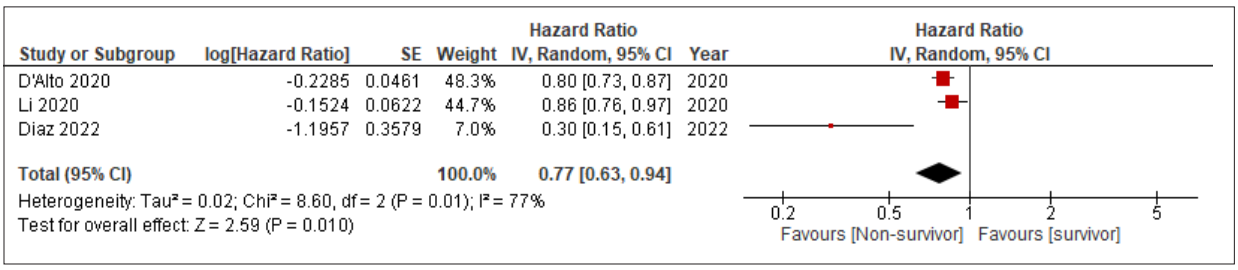

Fig. 4 — Association between TAPSE and mortality [unadjusted model].

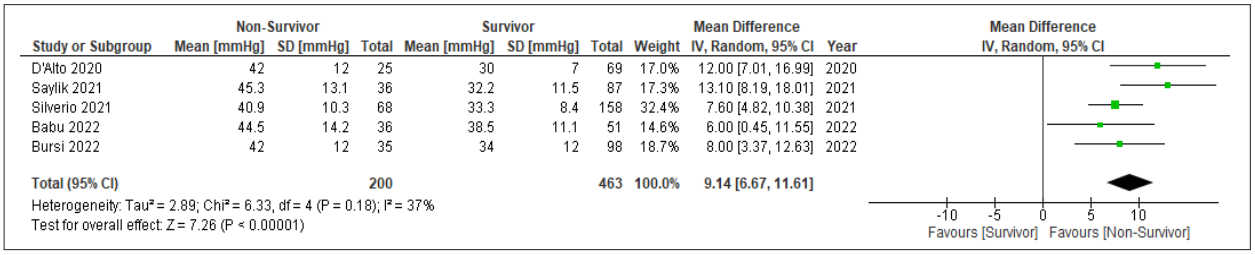

Fig. 5 — Mean difference in PASP between non-survivors and survivors.

mortality. However in a multivariate analysis, these variables were not significantly linked to in-hospital mortality (Table 1)[31]. In the fourth study, a receiver operating curve analysis was used for in- hospital death, yielding an area under the curve of 0.68 (95% CI, 0.55– 0.81; P=0.017) for TAPSE, and 0.71 (95% CI, 0.59– 0.83; P=0.005) for PASP35. Non-survivors had significantly worse RV characteristics, a higher PASP, and a lower TAPSE[35]. The fifth study found lower TAPSE and higher pulmonary valve acceleration time (PVAT), a measure of pulmonary pressure, to be significant for the outcome of mortality on the basis of univariable analysis, however on a multivariable analysis only PVAT emerged as significant (Table I)[36]. The sixth study revealed in a multivariable analysis of TAPSE and PASP that they were independently associated with in-hospital mortality (Table I)[37]. In the seventh study, a multivariable analysis found PASP> 35mmHg, RV FS of <35% and TAPSE < 17 mm to be associated with in-hospital mortality (Table I)[3]. In the eighth study, both lower TAPSE and increased PASP were significantly associated with mortality in an univariate analysis (Table I)[14]. In the ninth study, reduced TAPSE and RVFAC and increased PASP were found to be characteristics associated with in-hospital mortality[23]. However in a multivariate analysis, only PASP was significantly linked to in-hospital mortality (Table I)[23].

In three studies, reduced RV function or RV dysfunction but not RV afterload were independently associated with mortality[28,34,38]. However, in all 3 trials, PASP values were higher in the non-survivors than in the survivors[28,34,38]. One study used a multivariable analysis to determine the risk of in hospital mortality for both TAPSE and PASP, but only reduced TAPSE was found to be significantly associated with in hospital mortality (Table I)[28]. In the second study RV dysfunction was associated with a 3- fold increase in mortality but elevated PASP was not significantly associated with mortality (Table I)[34]. In the third study, right ventricular longitudinal strain (RVLS), right ventricular fractional area change (RVFAC), and TAPSE were all found to be independent risk factors for increased mortality in a multivariate analysis (Table I)[38].

Last, there was one study where a PASP > 35 mmHg as a parameter of RV afterload was the sole variable associated with death in a multivariable analysis (Table I)[30].

Meta-analysis showed that TAPSE was significantly lower in non-survivors compared with survivors (mean difference = – 3.53 [–4.72, –2.33], p < 0.00001; I2: 77%, p < 0.0005) [Figure 3]. In the pooled unadjusted model, lower TAPSE was associated with increased mortality (HR = 0.77 [0.63, 0.94], p < 0.010; I2: 77%, p = 0.01) [Figure 4]. Last, PASP was significantly higher in non-survivors compared with survivors (mean difference = 9.14 [6.67, 11.61], p < 0.00001; I2: 37%, p=0.18) [Figure 5].

Intensive Care Unit

Out of the 21 studies included in this review, only one study included both ICU and non-ICU patients in their study and analysed both groups regarding TAPSE, PASP or TAPSE/PASP. This study found through univariable logistic regression analysis that TAPSE in ICU patients (OR 0.79; 95% CI 0.68-0.92), TAPSE in non-ICU patients (OR 0.74; 95% CI 0.65-0.85), PASP in ICU patients (OR 1.09; 95% CI 1.02-1.15), PASP in non-ICU patients (OR 1.09; 95% CI 1.04-1.45), TAPSE/PASP in ICU patients (OR 0.01; 95% CI 0.0008-0.17) and TAPSE/PASP in non-ICU patients (OR 0.003; 95% CI 0.0002-0.05) were all significantly associated with a higher risk of mortality 37. As expected the ICU group showed a higher incidence of death (63.9 vs. 14.3%; p < 0.001), compared with non-ICU group[37].

Pulmonary embolism

Only one study evaluated the impact of RV-PA coupling on COVID-19 patients developing pulmonary embolism (PE) during their hospitalization37. They found through univariable logistic regression analysis that TAPSE/PASP (OR 0.01; 95% CI 0.001-0.09) was significantly associated with a higher risk of PE.

Table I. — Study characteristics 1/3.

Authors	Design	NOS	Sample size	Age (years)	Male (%)	ICU (%)	NIV (%)	MV (%)	TAPSE (mm)	PASP (mmHg)	RV-PA coupling (mm/mmHg)	Mortality (%)
Norderfeldt, 2021	Retrospective, observational	8	67 (non-aPH:41, aPH:26)	58 (34- 79)	94	100	16	84	non-aPH:21 (14-30), aPH:23.5 (15-31)	non-aPH:32 (22-35), aPH:50 (37-76)	NR	non-aPH:42, aPH:7
Saylik, 2021	Retrospective, observational	8	123	non-survivor:70.2 ± 9.8, survivor:62 ± 12.9	52	100	NR	NR	non-survivor:16.5 ± 4.4, survivor:20.7 ± 5.7	non-survivor:45.3 ± 13.1, survivor:32.2 ± 11.5	NR	in hospital: 29.3, *TAPSE (OR: 0.861, 95% CI 0.792–0.935, p<0.001), *RVFAC (OR: 0.837, 95% CI 0.764–0.917, p<0.001) *PASP (OR: 1.088, 95% CI 1.048–1.130, p<0.001), **TAPSE (OR: 0.949, 95% CI 0.862–1.044, p=0.280), **PASP (OR: 1.069, 95% CI 1.026–1.114, p=0.001)
Wats, 2021	Retrospective ,observational	9	214	66.5 ± 16.51	63.1	NR	NR	55.1	NR	NR	NR	30-day: 42.5, **mildly reduced RV systolic function (OR: 3.51, 95% CI 1.63–7.57, p=0.001), **moderate to severely reduced RV systolic function (OR: 7.30, 95% CI 2.20–24.25, p=0.001) and **PH (OR: 5.39, 95% CI 1.96–14.86, p=0.001)
Holmqvist, 2022	multicentre, observational	7	132	63 (53– 70)	74	100	3	86	normal:20 (19–23), LVD:20 (17– 22), RVD:15 (12– 16)	NR	NR	30-day: 18, *RVD on admission (OR 7.03, p=0.002), *RVD detected at any time in the ICU (OR 3.98, p=0.013), *PAP (OR 3.88, p=0.007)
Norden, 2021	Prospective, observational	9	31	58 (29-76)	77	100	0	100	21 ± 3	PASP>45 in 38%	NR	30-day: 10, in ICU: 19
Doyen, 2021	Prospective, observational	5	43	60 ± 13	84	100	NR	95	20 ± 5	26 ± 10	NR	14-day: 9
Silverio, 2021	multicentre, retrospective, observational	9	226	68.9 ± 13.9	62.4	31.9	43.8	29.6	20.5 ± 4.3	35.5 ± 9.7	NR	in hospital: 30.1, **TAPSE (RR: 0.80, 95% CI 0.72-0.88, p<0.001)

Table I. — Study characteristics 2/3.

Jain, 2021	Retrospective, observational	9	52	59.9 ± 11.6	60	100	NR	NR	18.12 (17.39 - 22.7)	PASP>40 in 19%	NR	in hospital: 27
Garcia-Cruz, 2020	cross-sectional	9	82	56 (50–66)	62.2	100	NR	79	19 (17–20)	32 (30–40)	NR	in hospital: 40.7, **PASP >35 mmHg (OR 11.7, 95% CI 2.28-60.1, P < 0.001)
Diaz, 2022	Prospective, observational	9	153	60.7 ± 14.1	69.3	100	NR	92.8	20 ± 2.9	PASP>35 in 22.2%	NR	60-day: 59.5, *TAPSE (HR 0.30, 95% CI 0.15 - 0.61, p<0.001), *PASP (HR 1.37, 95% CI 1.10 - 1.72, p=0.006), *RVDD (HR 1.53, 95% CI 0.98 – 2.39, p=0.060)
Lopez, 2022	cross-sectional	7	33	63.5 (60-80)	57	100	0	100	TAPSE≥17 in 6%	PASP>40 in 6%	NR	in ICU: 48
Gomez, 2022	Retrospective, observational	9	427	61.87 (15.03)	57	NR	NR	48	19.75 (5.46)	38.58 (15.11)	NR	60-day: 26, Abnormal RV function (OR 0.92, 95% CI 0.57-1.49, p=0.74)
Babu, 2022	Retrospective, observational	6	87	62.5±14.8	55.2	58.6	NR	NR	NR	41.7±13.1	NR	41.4, *RVD (OR: 2.97, 95% CI 1.11 - 7.94, p<0.03), *elevated PASP (OR 1.84, 95% CI 0.56 - 6.05, p=0.317)
Bursi, 2022	Prospective, observational	9	133	69±12	57	NR	77	9	21±5	36±12	TAPSE/PASP= 0.66±0.31	in hospital: 26
Bioh, 2022	Retrospective and prospective, observational	8	120	66.9±16.5	67	NR	NR	41.2	25±3.4	40.5±16.2	NR	27.5, **PVAT (HR 0.981, 95% CI 0.964 - 0.999, p=0.036)
Polito, 2021	multicentre, retrospective, observational	9	227	70 (60-79)	62.6	32.2	44.1	30	21 (18-23)	33 (30-40)	TAPSE/PASP ≤0.5 (n=78), 0.5<TAPSE/ PASP≤ 0.72 (n=73), TAPSE/PASP >0.72 (n=76)	in hospital: 30.1, **TAPSE (OR 0.85, 95% CI 0.74 - 0.97, P=0.017), **PASP (OR 1.08, 95% CI 1.03 - 1.13, p=0.002), **TAPSE/ PASP (OR 0.02, 95% CI 0.002 - 0.2, p <0,001)
Li, 2020	Prospective, observational	8	120	61±14	48	21	5	12.5	22.9±3.6	31 (24–45)	NR	15, **RVLS (HR 1.33, 95% CI 1.15 - 1.53, p < 0.001), **RVFAC (HR 0.90, 95% CI 0.83 - 0.98, p = 0.017), and **TAPSE (HR 0.88, 95% CI 0.78 - 0.99, p = 0.044)

Table I. — Study characteristics 3/3.

Manzur, 2021	cross-sectional	9	204	59 (48–67)	59.3	100	NR	82.5	19 (17—21)	30 (25–37)	TAPSE/ PASP= 0.6 (0.45–0.77)	in hospital: 37.6, **PASP> 35 (OR 5.82, p = 0.00), **RV FS of <35% (OR 3.4, p = 0.01), **TAPSE < 17 (OR 3.06, p = 0.01) and **TAPSE/PASP < 0.3 (OR 17.8, p = 0.00)
Bleakly, 2020	retrospective, observational	9	90	52.0 ± 10.8	74.4	100	0	100	20.0(4.8)	NR	RV FAC/ RVSP: 0.7 ± 0.3 %/mmHg	NR
D'Alto, 2020	Prospective, observational	8	94	survivors: 62 ± 13, non-survivors: 68 ± 12	survivors: 77, non-survivors: 68	100	23	39	survivors: 25 ± 4, non-survivors: 25 ± 4	survivors: 30 ± 7, non-survivors: 42 ± 12	survivors: TAPSE/PASP 0.89 ± 0.29, non-survivors: TAPSE/PASP 0.51 ± 0.22	27, **TAPSE/PASP (HR 0.026, 95% CI 0.01-0.579, p=0.019), *TAPSE (HR 0.796, 95% CI 0.727–0.871, p<0.001), *PASP (HR 1.085, 95% CI 1.054–1.118, p<0.001)
Rifaie, 2022	Prospective, observational	8	96	59.58 ± 8.63	71.9	NR	NR	NR	19.71 ± 2.35	RVSP: 36.34 ± 8.62	NR	3.1

Intensive Care Unit admission, Intensive Care Unit length of stay and mechanical ventilation duration

Unfortunately, the majority of the reviewed studies provided no information on the impact of RV-PA coupling on ICU admission, ICU length of stay, or mechanical ventilation duration. As a result, we were unable to assess these secondary outcomes.

Risk of Bias

Supplementary Table I shows the evaluation of every item of the NOS risk of bias tool. The selection of the cohorts in all included studies was adequate and somewhat representative. The outcome of interest was not present at the start of the studies. 16 out of 21 studies adjusted for multiple additional factors (e.g. age, sex, PaO_2/FiO_2). 5 studies did not adjust for any factor. The outcomes were assessed by record linkage. Only one study had an inadequate follow-up period of 14-days. 15 studies met the adequacy of follow-up of cohorts as 6 studies failed to mention it.

Discussion

COVID-19 non-survivors have a significantly worse RV-PA coupling, RV function and RV afterload as compared to survivors according to our meta-analysis. Individual studies suggested a higher risk of mortality for worse RV-PA coupling in both ICU and non-ICU patients as well as a higher risk of PE for worse RV-PA coupling.

The TAPSE/PASP ratio has been demonstrated to improve prediction accuracy in a number of clinical scenarios, including chronic heart failure with either a reduced or intact ejection fraction, pulmonary arterial hypertension, and PE[35]. Pulmonary hypertension is the main factor contributing to RV dysfunction in severe COVID-19 cases (PH). On the other hand, the RV is particularly vulnerable to SARS-CoV-2 infection and significant systemic inflammation can result in myocardial damage11.

RV dysfunction and elevated RV afterload are both independently associated with mortality[3,14,24,25,31,35-37]. Patients who had RV systolic dysfunction also had significantly higher PASP values, and those who had higher PASP were more likely to have TAPSE impairment, supporting the idea that the RV is susceptible to an increase in afterload9. Initially, when PH develops, the RV's contractility rises in response to a noticeably higher afterload[11]. An increased TAPSE might also occur in response to this11. TAPSE might not, however, be associated with an increase in pulmonary artery pressure in patients with persistent and progressive PH[41]. In this scenario, even a slight increase in afterload may cause a decrease in the RV's contractility, which

may be accompanied by a decrease in TAPSE[11]. Therefore, it is crucial to assess TAPSE and the TAPSE/PASP ratio in COVID-19. In line with the observational studies, TAPSE/PASP showed stronger predictive significance than either right ventricular function (TAPSE) alone or PASP alone, indicating that it is a valuable independent marker rather than just a ratio of two primary effects that can be modeled independently[3,14,35,37].

The majority of studies used TAPSE, an echocardiographic parameter for the longitudinal function of the RV, to assess RV function. One study suggested a better parameter for measuring RV function in COVID-19 patients[39]. They believe that the predominant RV characteristic in COVID-19 patients is RV radial dysfunction rather than longitudinal dysfunction, hence RVFAC rather than TAPSE should be used to assess RV function[39]. In this study, patients with COVID-19 had decreased mean RV systolic function as measured by RV FAC (28.9±10.6%), while TAPSE (20 ± 4.8 mm), was preserved[39]. Compared to TAPSE, RV FAC detected RV dysfunction in a much larger percentage of individuals39. Additionally, by using the ratio of RV FAC/RVSP in preference to TAPSE/PASP in its cohort of 90 patients to determine RV-PA coupling, they identified 85.9 (95% CI 75.4–92.4)% of patients as having RV-PA uncoupling (n = 64)[39]. TAPSE's measurement of long-axis function was unable to detect the study's high RV impairment load[39]. Because of this, relying just on longitudinal parameters to interpret RV health may miss the severity of the damage, and the particular phenotype they have found may be important in alerting clinicians to avoid interpretation solely based on longitudinal parameters[39]. It is important to note that both TAPSE/PASP and RV FAC/RVSP are an oversimplification of the concept of RV-PA coupling. The gold standard of measuring RV-PA coupling remains the Ees/Ea ratio using intraventricular conductance catheters[13,42-44].

When comparing ICU patients to non-ICU patients, a study by Polito et al. found that TAPSE, PASP and TAPSE/PASP were all significantly associated with a higher risk of death in both ICU and non-ICU patients, respectively. This illustrates the value of stratifying the risk of mortality using TTE measurement of RV and pulmonary pressure in both ICU and non-ICU patients.

Clinical implications

We found that an RV-PA coupling impairment is directly or indirectly related to a poor prognosis in COVID-19. It has been demonstrated previously that early echocardiographic assessment of RV-PA coupling can offer helpful insights for clinical management in individuals with clinical suspicion of heart issues[3,14,35]. Also, in identifying COVID-19 patients at high risk, a multiparametric evaluation could include the TAPSE/PASP ratio. Further studies are warranted to investigate whether therapies specifically aiming at an improvement of RV-PA coupling (e.g., by lowering RV afterload, increasing RV contractility, or both) can improve the dismal prognosis of patients with severe COVID-19.

Study limitations

First, retrospective studies made up almost half of the studies, which itself could be a source of bias. Second, the limited number of studies used in the meta-analysis and the low number of patients included, makes it difficult to extend our findings to the entire COVID-19 population. Third, the reporting of outcomes varied between studies, with primary and secondary endpoints being assessed at various time points. Fourth, to conduct a more thorough meta-analysis and to assess secondary outcomes that have not been included in this study, additional larger prospective studies are needed. Unfortunately, due to a paucity of reported data on length of stay or duration of mechanical ventilation, we were unable to assess the effect of RV-PA coupling on these outcomes. Fifth, the provided data did not match the requirements for a diagnostic test meta-analysis, which, had it been disclosed, would have been helpful for determining the post-test risk of mortality in patients with TAPSE/PASP below a certain cut-off value[9]. Sixth, of the studies included in this systematic review, we only analyzed those that included ICU patients in their study population. Some studies did not mention patients' admission status. Therefore, these were not part of the current meta-analysis. As a result, our findings cannot be generalized to the entire COVID-19 population. Seventh, a potential contributor to between study heterogeneity was the varying timing of the echocardiogram in relation to the progression of the disease.

Conclusion

This systematic review and meta-analysis evaluated the effect of RV-PA coupling in patients with COVID-19 on morbidity and mortality. According to our meta-analysis COVID-19 non-survivors have a significantly worse RV-PA coupling as compared to survivors.

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