Received: 13 May 2021 | Revised: 22 June 2021 | Accepted: 31 July 2021

DOI: 10.1111/echo.15175

Echocardiography WILEY

ORIGINAL ARTICLE

Relationship between echocardiographic tricuspid annular plane systolic excursion and mortality in COVID-19 patients: A Meta-analysis

Marco Zuin MD[1] | Gianluca Rigatelli MD PhD[2] | Loris Roncon MD[2] | Giovanni Zuliani MD PhD[1]

[1] Department of Translational Medicine, University of Ferrara, Ferrara, Italy

[2] Department of Cardiology, Rovigo General Hospital, Rovigo, Italy

Correspondence
Marco Zuin MD, Department of Translational Medicine, Section of Internal and Cardio Respiratory Medicine, University of Ferrara, Ferrara 44100, Italy.
Email: zuinml@yahoo.it; marco.zuin@edu.unife.it

Abstract

Background: The evaluation of the tricuspid annular plane systolic excursion (TAPSE) is recommended to assess the right ventricular (RV) systolic function. We performed an updated meta-analysis of the association between TAPSE and short-term mortality in COVID-19 patients.

Methods: MEDLINE and Scopus databases were searched to locate all the articles published up to May 1, 2021, reporting data on TAPSE among COVID-19 survivors and non-survivors. The difference of TAPSE between the two groups was expressed as mean difference (MD) with the corresponding 95% confidence interval (CI) using the Mantel-Haenszel random effects model. Both Q value and I^2 statistics were used to assess heterogeneity across studies. Sensitivity analysis, meta-regression, and evaluation of bias were performed.

Results: Twelve studies, enrolling 1272 COVID-19 patients (778 males, mean age 69.3 years), met the inclusion criteria and were included in the final analysis. Non-survivors had a lower TAPSE compared to survivors (MD = −3.089 mm, 95% CI = −4.087 to −2.091, $p < 0.0001$, $I^2 = 79.0\%$). Both the visual inspection of the funnel plot and the Egger's tests (t = 1.195, $p = 0.259$) revealed no evidence of publication bias. Sensitivity analysis confirmed yielded results. Meta-regression analysis evidenced that the difference in TAPSE between the two groups was only influenced by pre-existing chronic obstructive pulmonary disease (COPD, $p = 0.02$).

Conclusion: COVID-19 non-survivors have a lower TAPSE when compared to survivors, especially in COPD subjects. Current data suggest that the TAPSE assessment may provide useful information regarding the short-term prognosis of COVID-19 patients during the infection.

KEYWORDS
COVID-19, echocardiography, mortality, TAPSE

 © 2021 Wiley Periodicals LLC

1 | INTRODUCTION

Right ventricular function represents an important prognostic predictor for several cardiovascular disease.[1–4] However, its accurate estimation, in both normal and pathological conditions, remains difficult due to the peculiar geometry of the right ventricle (RV).[3,4] The American Society of Echocardiography recommend to routinely use the tricuspid annular phase systolic excursion (TAPSE) to evaluate the RV systolic function.[5] In this regard, recent analyses have demonstrated that the echocardiographic assessment of RV function represents a useful parameter for the prognostication of COVID-19 patients.[6–8] Indeed, both RV size and function play a pivotal role in the pathogenesis of cardiovascular complications in COVID-19 patients.[9] However, EIR assessment in these subjects, is not routinely performed in daily clinical practice. Aim of the present manuscript is to perform an updated analysis on the association between TAPSE and short-term mortality in COVID-19 patients.

2 | METHODS

2.1 | Data sources and searches

The study was performed in accordance with the Preferred Report Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[10] The PRISMA checklist is reported in *Supplementary file 1*. MEDLINE and Scopus databases were systematically searched for articles, published in English language, from inception through May 1, 2021 with the following Medical Subject Heading (MESH) terms: COVID-19 [Title/Abstract] AND Right ventricle [Title/Abstract] or TAPSE [Title/Abstract] to locate articles providing TAPSE data, stratified among survivors and non-survivors. Moreover, references from the included studies were screened to potentially identify other investigations meeting the inclusion criteria. Ethical approval and informed consent were not required as the study did not directly enroll human subjects.

2.2 | Study selection

Specifically, inclusion criteria were: (i) studies enrolling subjects with a confirmed diagnosis of COVID-19; (ii) studies stratifying the population as survivors and non-survivors; and (iii) providing echocardiographic data on TAPSE. Conversely, case reports, review articles, editorials/letters, and case series with less than 10 participants, and randomized controlled trials were excluded. Two reviewers (M.Z., G.Z.) independently evaluated each included article; in case of discrepancies a third author was involved (G.R.) and final consensus was achieved through discussion.

2.3 | Data extraction and quality assessment

Data were independently extracted by two reviewers (C.B.; L.R.) using a standardized protocol. Disagreements were resolved through discussion. For this meta-analysis, the following data elements were extracted: sample size, mean age, gender, number of NS and major comorbidities, such as arterial hypertension, diabetes mellitus, pre-existing coronary artery disease and chronic obstructive pulmonary disease (COPD). Moreover, due the potential heart-lung interactions during respiratory support, also the number of patients requiring non-invasive (NIV) and invasive (IMV) mechanical ventilation were retrieved from the revised manuscripts. The quality of the included studies was graded using the Newcastle–Ottawa quality assessment scale (NOS).[11]

2.4 | Outcomes

The mortality risk related to TAPSE in COVID-19 patients was chosen as the primary outcome of the study.

2.5 | Data synthesis and analysis

Continuous variables were expressed as mean ± standard deviation (SD) or as median with corresponding inter-quartile range while categorical variables as counts and percentages. The difference of TAPSE between non-survivors and survivors was expressed as mean difference (MD) with the corresponding 95% confidence interval (CI) using a random-effect model. Q value and I^2 statistics were used to assess heterogeneity across studies Specifically, a $I^2 = 0$ was considered to indicate no heterogeneity while values of I^2 as < 25%, 25–75% and above 75% to indicate low, moderate, and high degrees of heterogeneity, respectively.[12] A predefined sensitivity analysis (leave-one-out analysis) was performed removing one study at the time. To evaluate the presence of publication bias both funnel plot and Egger's test were computed. To further appraise the impact of potential baseline confounders, a meta-regression analysis using the patient's clinical characteristics, comorbidities and type of respiratory support (if any) were used as moderator variables. All meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA).

3 | RESULTS

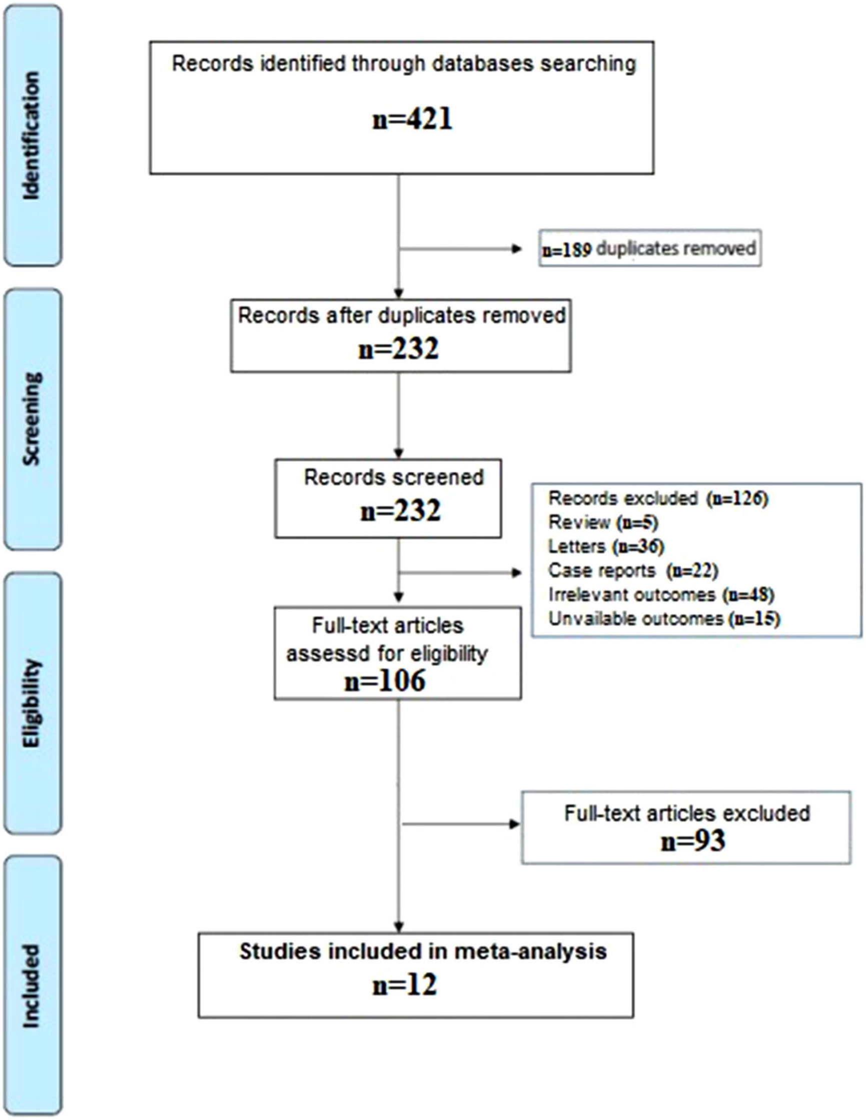
3.1 | Search results

A total of 421 articles were identified using our search strategy. After removing duplicates, 126 studies were excluded based on their title and/or abstract. Then, screening of the full texts of the remaining 106 articles identified 12 investigations [13–24] that met all the eligibility criteria, as showed in Figure 1.

3.2 | Population enrolled

Overall, 1272 COVID-19 patients (778 males, mean age 69.3 years) were analyzed. Baseline characteristics of the patients enrolled in

FIGURE 1 PRISMA flow-chart



each revised study are presented in Table 1. Mortality rate was 22.3% (n = 284). Among reported comorbidities, arterial hypertension and diabetes mellitus were the most common observed. Unfortunately, the prevalence of pre-existing coronary artery disease and COPD as well as the need for both NIV and MIV respiratory support were not systematically reported by the reviewed manuscripts. Quality assessment showed that all the studies were of moderate-high quality according to the NOS scale (Table 2).

3.3 | TAPSE and mortality risk

Non-survivors had a lower TAPSE compared to survivors (MD = −3.089 mm, 95% CI = −4.087 to −2.091, $p < 0.0001$, $I^2 = 79.0\%$) (Figure 2). Both the visual inspection of the funnel plot (Supplementary file 2) and the Egger's tests (t = 1.195, $p = 0.259$) revealed no evidence of publication bias.

3.4 | Sensitivity analysis

One-by-one exclusion of the studies from the analysis slightly changed the combined MD, which remained statistically significant across a range from −2.921 (95% CI: −4.124 to −1.732, I^2:74.9%) to −3.313 (95% CI: −4.350 to −2.275, I^2:79%), suggesting that no single study had an undue impact on the combined MD.

3.5 | Meta-regression

Meta-regression analysis evidenced that the difference in TAPSE between non-survivors and survivors was influenced by pre-existing COPD ($p = 0.02$). Conversely, no interactions were observed using age ($p = 0.39$), male gender ($p = 0.66$), arterial hypertension ($p = 0.98$), diabetes mellitus ($p = 0.74$), pre-existing coronary artery disease ($p = 0.83$), NIV ($p = 0.28 =$ and IMV ($p = 0.30$) (Table 3).

TABLE 1 General characteristics of the population enrolled

Author	Demographics				Comorbidities				Respiratory support	
	Patients enrolled N	Mean age (years) [IQR]	Males N (%)	NS N (%)	HT N (%)	DM N (%)	CAD N (%)	COPD N (%)	NIV N (%)	IMV N (%)
D'Alto et al.[13]	94	S: 62±62±13 NS: 68±12	70 (74.4)	25 (26.3)	63 (67.0)	16 (17.0)	17 (18.0)	NR	12 (23.4)	37 (39.3)
Lazzeri et al.[14]	47	63±11	39(82.9)	13 (27.6)	41 (87.0)	15 (32.0)	NR	3 (6)	12 (25.0)	37 (75)
Stockenhuber et al.[15]	34	72±2.6	27 (79)	15 (44.1)	(53)	(35)	11 (22.4)	NR	NR	NR
Bursi et al.[16]	49	65.7±12.6	31 (63.3)	16 (32.6)	24 (48.9)	9 (18.4)	11 (22.4)	6 (12.2)	NR	NR
Lassen et al.[17]	214	S: 67.7±13.5 NS:78.5±9.0	117 (54.6)	25 (11.6)	122 (57.0)	54 (25.2)	NR	32 (14.9)	NR	NR
Xie et al.[18]	132	61±13	68 (51.5)	19 (14.3)	58 (43.9)	15 (11.4)	19 (14.4)	5 (3.8)	10 (7.6)	22 (16.7)
Zhang et al.[19]	128	61.3±13.1	61 (47.7)	18 (14.1)	52 (40.6)	18 (14.1)	NR	7 (5.5)	9 (7.0)	17 (13.3)
Liu et al.[20]	43	64.5±10.0	22 (51.2)	22 (51.2)	19 (44.2)	12 (27.9)	5 (11.6)	NR	NR	39 (90.7)
Badkoubeh e t al.[21]	86	58.8 [16–86]	52 (60.5)	11 (12.7)	36 (41.9)	29 (33.7)	21 (24.4)	3 (3.5)	NR	NR
Li (1) et al.[22]	120	61±14	57 (47.5)	18 (15.0)	48 (40.0)	14 (11.7)	11 (9.2)	6 (5.0)	6 (5.0)	15 (12.5)
Li (2) et al.[23]	89	66±11	79 (50.3)	20 (22.4)	70 (44.6)	23 (14.6)	26 (16.6)	9 (5.7)	11 (7.0)	26 (16.6)
Duclos et al.[24]	57	62±14	44 (77.1)	12 (21.0)	28 (49.1)	22 (38.5)	10 (17.5)	NR	NR	40 (70.1)

Abbreviations: NS, Non -survivors; HT, Arterial hypertension; DM, Diabetes Mellitus; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; NIV, Non-invasive mechanical ventilation; IMV, Invasive mechanical ventilation

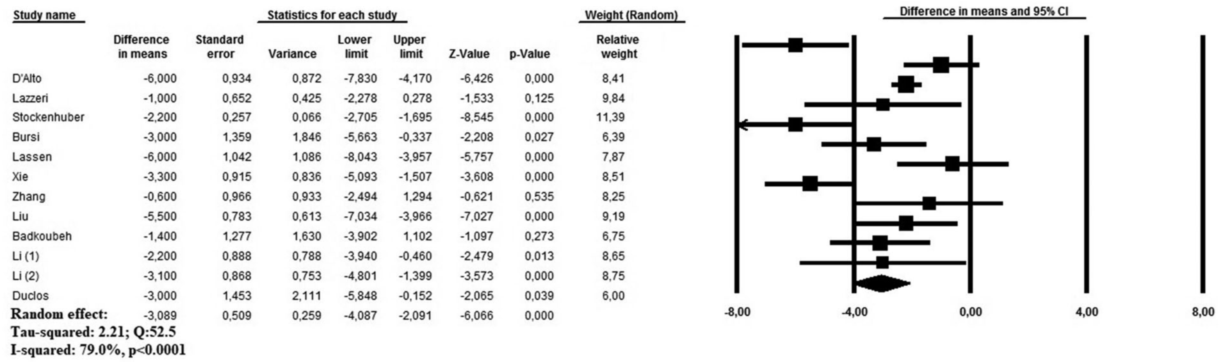


FIGURE 2 Forest plot investigating the mean difference of TAPSE among COVID-19 survivors and non-survivors

TABLE 2 Quality of the included studies assessed using the Newcastle-Ottawa quality assessment scale (NOS)

Study	NOS			
	Selection	Compar-ability	Outcome	Total score
D'Alto et al.[13]	***	**	***	8
Lazzeri et al.[14]	***	**	***	8
Stockenhuber et al.[15]	***	**	**	7
Bursi et al.[16]	***	**	**	7
Lassen et al.[17]	***	**	***	8
Xie et al.[18]	***	**	**	7
Zhang et al.[19]	***	**	***	8
Liu et al.[20]	***	**	***	8
Badkoubeh et al.[21]	***	**	***	8
Li (1) et al.[22]	***	***	**	8
Li (2) et al.[23]	***	***	**	8
Duclos et al.[24]	***	**	**	7

4 | DISCUSSION

Our results suggested that COVID-19 non-survivors have a lower TAPSE when compared to survivors. Therefore, this echocardiographic parameter should be considered as an additional prognostic tool for subjects with SARS-CoV-2 infection. It has already been demonstrated that echocardiography as non-invasive, portable imaging tool, can provide valuable information regarding the hemodynamic function and prognosis in several disease.[25] Furthermore, TAPSE can be easily evaluated at bedside and thanks to its low inter-observer variability, represents a well-established method for the assessment of RV function.[26]

Our findings, which represent an update on the prognostic role of TAPSE in COVID-19 patients, are in accordance with a previous meta-analysis, performed on a small sample, on this issue performed by Martha et al.[27]. These authors included in their analysis only six investigations[13,17,18,21–23] enrolling 641 patients. Conversely, our analysis, adding other six subsequent studies,[14,16,19,20,21,25] doubled the analyzed sample, ameliorating the estimation of TAPSE difference between S and NS and allowing a more precise evaluation of potential publication bias using also the Egger's test which is recommended in those meta-analysis considering more than ten studies.[28] Despite also our meta-regression evidenced that pre-existing COPD affected the difference in TAPSE between COVID-19 non-survivors and survivors analysis, we additionally considered as moderating variables NIV and IMV. Indeed, as previously reported by different analyses, both the type and characteristics of respiratory support may influence the TAPSE estimation.[29–31] Therefore, the high heterogeneity observed in our analysis may be explained by the influence of pre-existing COPD, the design of reviewed studies and associated inherited bias.

Our results further emphasize the prognostic role of echocardiography in COVID-19 patients.[31] In this regard, several recent investigations have mainly focused their attention on the prognostic impact of speckle tracking analysis.[17,18,22,33] However, such type of evaluation required specialistic abilities as well as dedicated software. Conversely, TAPSE can be easily assessed bedside also by physicians having basic echocardiographic skills.

As a matter of a fact, it has been demonstrated that COVID 19-induced ARDS is associated with early and pronounced uncoupling of RV function from the pulmonary circulation and that the ratio between TAPSE and pulmonary arterial systolic pressure (PASP) ratio adds significantly and independently to the prognostic relevance of the PaO2/FIO2 ratio in these patients, highlighting the role of bedside echocardiography assessment in COVID-19 patients requiring intensive care.[13]

The results provided by our update analysis suggest some clinical implications in daily practice. Firstly, a low TAPSE must raise the suspicion of underling cardiac abnormality/injury which may affect the clinical course of the COVID-19 and must, therefore, be identified. Secondly, low TAPSE value may be considered as an earlier manifestation of cardiac involvement or complications in COVID-19 patients, recommending the need for a closer monitoring due the higher risk of short-term mortality. Indeed, Marhta et al. have estimated that every 1 mm decrease in TAPSPE was associated with a 20% higher mortality risk.[27]

TABLE 3 Meta regression analysis

	No of Interactions	Meta regression Coeff	SE	95% CI	*p*
Age	12	.003	.003	-.004 to .011	0.39
Males	12	.017	.040	-.061 to .096	0.66
HT	12	-.0008	.038	-.076 to .074	0.98
DM	12	.019	.058	-.094 to .133	0.74
CAD	9	.026	.124	-.0217 to .269	0.83
COPD	8	-.305	.133	-.566 to -.044	0.02
NIV	6	.069	.064	-.057 to .196	0.28
IMV	8	.020	.020	-.019 to .060	0.30

Abbreviations: HT, Arterial hypertension; DM, Diabetes mellitus; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; NIV, Non-invasive mechanical ventilation; IMV, Invasive mechanical ventilation

4.1 | Limitations

Our analysis has some important limitations that must be recognized. In fact, the observational and retrospective nature of the reviewed studies and their intrinsic and inherited biases may have result in not firm conclusions. Selection bias as well as the absence of adequate control over different variables which may have influenced the TAPSE did not allow us to make any conclusion regarding, for example, patients dying due to respiratory failure or related to a worse RV function. At the same manner, none of the revised studies provided any data regarding the follow-up. Moreover, our analysis was not able to discriminate and/or compare the TAPSE value with previous echocardiographic assessment before COVID-19 infection. Furthermore, we cannot evaluate a TAPSE threshold associated with a poor outcome in the short-term period; in this regard further analysis are required. Finally, the different treatment strategies and/or cardiovascular drugs/support may have influenced the TAPSE value in both groups.

5 | CONCLUSIONS

COVID-19 non-survivors have a lower TAPSE when compared to survivors. Current data suggest that the TAPSE assessment may provide useful information regarding the short-term prognosis of COVID-19 patients during the infection. A low TAPSE value suggest a closer cardiac monitoring in such patients since an impaired RV function influence the COVID-19 patient's outcome.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

ORCID

Marco Zuin MD https://orcid.org/0000-0002-4559-1292

REFERENCES

1. Zornoff LAM, Skali H, Pfeffer MA, et al. Right ventricular dysfunction and risk of heart failure and mortality after myocardial infarction. *J Am Coll Cardiol*. 2002;39:1450-1455.
2. Voelkel NF, Quaife RA, Leinwand LA, et al. National heart, lung, and blood institute working group on cellular and molecular mechanisms of right heart failure. right ventricular function and failure: report of a national heart, lung, and blood institute working group on cellular and molecular mechanisms of right heart failure. *Circulation*. 2006;114:1883-1891.
3. Greyson CR. Evaluation of right ventricular function. *Curr Cardiol Rep*. 2011;13:194-202.
4. Jurcut R, Giusca S, La Gerche A, Vasile S, Ginghina C, Voigt J-U. The echocardiographic assessment of the right ventricle: what to do in 2010?. *Eur J Echocardiogr*. 2010;11:81-96.
5. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685-713.
6. Shahrbaf MA, Tabary M, Khaheshi I. The right ventricle in COVID-19 patients. *Eur Heart J*. 2021;42:559-560.
7. Moody WE, Mahmoud-Elsayed HM, Senior J, et al. Impact of right ventricular dysfunction on mortality in patients hospitalized with COVID-19, according to race. *CJC Open*. 2021;3:91-100.
8. Pellikka PA, Naqvi TZ. The right ventricle: a target in COVID-19 cardiac insult. *J Am Coll Cardiol*. 2020;76:1978-1981.
9. Park JF, Banerjee S, Umar S. In the eye of the storm: the right ventricle in COVID-19. *Pulm Circ*. 2020;10:2045894020936660.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
11. Wells GA, Shea B, O'Connell D, et al, The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses, 2012. http://wwwohrica/programs/clinical_epidemiology/oxfordasp, Accessed: May 4, 2020
12. Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
13. D'alto M, Marra AM, Severino S, et al. Right ventricular-arterial uncoupling independently predicts survival in COVID-19 ARDS. *Crit Care*. 2020;24:670.
14. Lazzeri C, Bonizzoli M, Batacchi S, Socci F, Matucci-Cerinic M, Peris A. Combined lung and cardiac ultrasound in COVID-related acute

respiratory distress syndrome. *Intern Emerg Med*. 2021;11:1-7. https://doi.org/10.1007/s11739-021-02646-7
15. Stockenhuber A, Vrettos A, Androschuck V, et al. A pilot study on right ventricular longitudinal strain as a predictor of outcome in COVID-19 patients with evidence of cardiac involvement. *Echocardiography*. 2021;38:222-229.
16. Bursi F, Santangelo G, Sansalone D, et al. Prognostic utility of quantitative offline 2D-echocardiography in hospitalized patients with COVID-19 disease. *Echocardiography*. 2020;37:2029-2039.
17. Lassen MCH, Skaarup KG, Lind JN, et al. Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. *ESC Heart Fail*. 2020;7:4189-4197.
18. Xie Y, Wang L, Li M, et al. Biventricular longitudinal strain predict mortality in COVID-19 patients. *Front Cardiovasc Med*. 2021;7:632434.
19. Zhang Y, Sun W, Wu C, et al. Prognostic value of right ventricular ejection fraction assessed by 3D echocardiography in COVID-19 patients. *Front Cardiovasc Med*. 2021;8:641088.
20. Liu Y, Xie J, Gao P, et al. Swollen heart in COVID-19 patients who progress to critical illness: a perspective from echo-cardiologists. *ESC Heart Fail*. 2020;7:3621-3632.
21. Sattarzadeh Badkoubeh R, Khoshavi M, Laleh Far V, et al. Imaging data in COVID-19 patients: focused on echocardiographic findings. *Int J Cardiovasc Imaging*. 2021;37:1629-1636.
22. Li Y, Li H, Zhu S, et al. Prognostic value of right ventricular longitudinal strain in patients with COVID-19. *JACC Cardiovasc Imaging*. 2020;13:2287-2299.
23. Li Y, Fang L, Zhu S, et al. Echocardiographic characteristics and outcome in patients with COVID-19 infection and underlying cardiovascular disease. *Front Cardiovasc Med*. 2021;8:642973.
24. Duclos G, Bazalguette F, Allaouchiche B, et al. Can thoracic ultrasound on admission predict the outcome of critically ill patients with SARS-CoV-2? A French multi-centric ancillary retrospective study. *Adv Ther*. 2021:1-14.
25. Beigel R, Cercek B, Arsanjani R, Siegel RJ. Echocardiography in the use of noninvasive hemodynamic monitoring. *J Crit Care*. 2014;29:184. e1-8.
26. Kopecna D, Briongos S, Castillo H, et al. Interobserver reliability of echocardiography for prognostication of normotensive patients with pulmonary embolism. *Cardiovasc Ultrasound*. 2014;12:29.
27. Martha JW, Pranata R, Wibowo A, Lim MA. Tricuspid annular plane systolic excursion (TAPSE) measured by echocardiography and mortality in COVID-19: a systematic review and meta-analysis. *Int J Infect Dis*. 2021;105:351-356.
28. https://handbook-5-1.cochrane.org/chapter_10/10_4_3_1_recommendations_on_testing_for_funnel_plot_asymmetry.htm
29. Franchi F, Faltoni A, Cameli M, et al. Influence of positive end-expiratory pressure on myocardial strain assessed by speckle tracking echocardiography in mechanically ventilated patients. *Biomed Res Int*. 2013;2013:918548.
30. Goursaud S, Valette X, Dupeyrat J, Daubin C, Du Cheyron D. Ultraprotective ventilation allowed by extracorporeal CO2 removal improves the right ventricular function in acute respiratory distress syndrome patients: a quasi-experimental pilot study. *Ann Intensive Care*. 2021;11:3.
31. Zhang H, Wang X, Chen X, Zhang Q, Liu D. Tricuspid annular plane systolic excursion and central venous pressure in mechanically ventilated critically ill patients. *Cardiovasc Ultrasound*. 2018;16:11.
32. Rodríguez-Santamarta M, Minguito-Carazo C, Echarte-Morales J, Del Castillo-García S. Cardiac involvement in COVID-19: does echocardiography matter? *Response Rev Esp Cardiol (Engl Ed)*. 2021; 74:281.
33. Croft LB, Krishnamoorthy P, Ro R, et al. Abnormal left ventricular global longitudinal strain by speckle tracking echocardiography in COVID-19 patients. *Future Cardiol*. 2021;17:655-661. https://doi.org/10.2217/fca-2020-0121

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Zuin M, Rigatelli G, Roncon L, Zuliani G Relationship between echocardiographic tricuspid annular plane systolic excursion and mortality in COVID-19 patients: A Meta-analysis. *Echocardiography*. 2021;38:1579–1585. https://doi.org/10.1111/echo.15175