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

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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 I² 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, I² = 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
INTRODUCTION

Right ventricular function represents an important prognostic predictor for several cardiovascular disease. However, its accurate estimation, in both normal and pathological conditions, remains difficult due to the peculiar geometry of the right ventricle (RV). The American Society of Echocardiography recommend to routinely use the tricuspid annular phase systolic excursion (TAPSE) to evaluate the RV systolic function. 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. Indeed, both RV size and function play a pivotal role in the pathogenesis of cardiovascular complications in COVID-19 patients. 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.

METHODS

Data sources and searches

The study was performed in accordance with the Preferred Report Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. 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.

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.

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).

Outcomes

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

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 I² statistics were used to assess heterogeneity across studies. Specifically, a I² = 0 was considered to indicate no heterogeneity while values of I² as < 25%, 25–75% and above 75% to indicate low, moderate, and high degrees of heterogeneity, respectively. 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).

RESULTS

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 that met all the eligibility criteria, as showed in Figure 1.

Population enrolled

Overall, 1272 COVID-19 patients (778 males, mean age 69.3 years) were analyzed. Baseline characteristics of the patients enrolled in
The 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, I² = 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, I²:74.9%) to −3.313 (95% CI: −4.350 to −2.275, I²:79%), 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).
| Author          | Patients enrolled N | Demographics | Mean age (years) [IQR] | Males N (%) | NS N (%) | Comorbidities | Respiratory support |
|-----------------|---------------------|--------------|------------------------|-------------|----------|---------------|---------------------|
|                |                     |              |                        |             |          | HT N (%) | DM N (%) | CAD N (%) | COPD N (%) | NIV N (%) | IMV N (%) |
| D’Alto et al. 13 | 94                  | S: 62±62±13  | 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| 117 (54.6)             | 25 (116)    | 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 (14.7) |
| 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 et al. 21 | 86              | 58.8±16.8   | 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.
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 specialist 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 underlying 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, Martha et al. have estimated that every 1 mm decrease in TAPSE was associated with a 20% higher mortality risk.\(^{27}\)
### TABLE 3  Meta regression analysis

|         | No of Interactions | 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.

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

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