The Prognostic Value of Cardiac Biomarkers and Echocardiography in Critical COVID-19

Bert Zwaenepoel (bert.zwaenepoel@uzgent.be)
Ghent University: Universiteit Gent  https://orcid.org/0000-0003-3786-6222

Sebastiaan Dhont
Ghent University: Universiteit Gent

Eric Hoste
Ghent University: Universiteit Gent

Sofie Gevaert
Ghent University: Universiteit Gent

Hannah Schaubroeck
Ghent University: Universiteit Gent

Research

Keywords: COVID-19, cardiac injury, cardiac biomarkers, hs-cTnT, NT-proBNP, ICU

DOI: https://doi.org/10.21203/rs.3.rs-751788/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background Early risk stratification is crucial in critically ill COVID-19 patients. Myocardial injury is associated with worse outcome. This study aimed to evaluate cardiac biomarkers and echocardiographic findings in critically ill COVID-19 patients and to assess their association with 30-day mortality in comparison to other biomarkers, risk factors and clinical severity scores.

Methods Prospective, single-center, cohort study in patients with PCR-confirmed, critical COVID-19. Laboratory assessment included high sensitive troponin T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) on admission to ICU: a hs-cTnT $\geq$ 14 pg/mL and a NT-proBNP $\geq$ 450 pg/mL were considered as elevated. Transthoracic echocardiographic evaluation was performed within the first 48 hours of ICU admission. The primary outcome was 30-day all-cause mortality. Predictive markers for mortality were assessed by ROC analysis and cut-off values by the Youden Index.

Results A total of 100 patients were included. The median age was 63.5 years, the population was predominantly male (66%). At the time of ICU admission, 47% of patients had elevated hs-cTnT and 39% had elevated NT-proBNP. Left ventricular ejection fraction was below 50% in 19.1%. Elevated cardiac biomarkers (hs-cTnT P-value < 0.001, NT-proBNP P-value = 0.001) and impaired left ventricular function (P-value 0.011) were significantly associated with mortality, while other biomarkers (D-dimers, ferritin, C-reactive protein) and clinical scores (SOFA) did not differ significantly between survivors and non-survivors. An optimal cut-off value to predict increased risk for 30-day all-cause mortality was 16.5 pg/mL for hs-cTnT (OR 8.5, 95% CI: 2.9, 25.0) and 415.5 pg/ml for NT-proBNP (OR 5.1, 95% CI: 1.8, 14.7).

Conclusion Myocardial injury in COVID-19 is common. Early detection of elevated hs-cTnT and NT-proBNP are predictive for 30-day mortality in patients with critical COVID-19. These markers outperform other routinely used biomarkers, as well as clinical indices of disease severity in ICU. The additive value of routine transthoracic echocardiography is disputable and should only be considered if it is likely to impact therapeutic management.

Background

Currently, SARS-CoV-2 has infected over 190 million people, resulting in more than 4 million registered deaths (1). Based upon the severity of illness, the National Institutes of Health (NIH) proposes five categories: asymptomatic, mild, moderate, severe and critical. The latter contains individuals with respiratory failure, septic shock, and/or multiple organ dysfunction requiring intensive care (2).

Myocardial injury is common in Coronavirus Disease 2019 (COVID-19). The prevalence of values above the upper reference limit (URL) for high sensitive troponin (hs-cTnT) in COVID-19 patients varies widely, ranging from 20% in cohorts of hospitalized patients to more than 50% in critically ill patients (3–6). Data about natriuretic peptides are more scarce, though up to 48% of critical COVID-19 patients present with elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) (7). Echocardiographic abnormalities are observed in up to half of all COVID-19 patients undergoing echocardiography (8–10).
Elevated cardiac biomarkers and echocardiographic abnormalities, especially reduced ventricular contractility, are associated with worse clinical outcome including mortality in COVID-19 patients (7, 10–15). As most of the published reports are retrospective studies, the current role of cardiac biomarkers and/or echocardiography in the prognostication of COVID-19 patients is still unclear. Different cardiac societies therefore have recommended against the routine use of these parameters for prognostic purposes (16, 17).

The purpose of this study was to prospectively evaluate the presence of elevated cardiac biomarkers and echocardiographic abnormalities in critical COVID-19 patients at the time of admission to the intensive care unit (ICU), to assess their association with 30-day all-cause mortality and to compare their prognostic performance to that of other biomarkers, risk scores and risk factors.

Methods

Study design, data collection and study outcome

This prospective, single-center, cohort study was carried out at the ICU of the Ghent University Hospital in Belgium, a 1.061-beds tertiary care center, between April 2020 and April 2021. The study was approved by the local ethical committee (BC-07568, April 1st, 2020). Inclusion criteria were: age 18 years or older, ICU admission, severe COVID-19 as diagnosed by real-time reverse-transcriptase polymerase chain reaction assays, and informed consent of the patient or legal representative. Patients were included within 48 hours after ICU admission. Patients were excluded when informed consent for this study was not obtained or when they were transferred from other ICUs of surrounding hospitals. Given the fact that COVID-19 is a new disease and the explorative character of the study, we decided to limit the number of included patients to a convenience sample of 100 patients.

Demographics, pre-existing comorbidities and clinical risk-scores and ratios (total and respiratory sequential organ failure assessment score (SOFA) and PaO2/FiO2-ratio (P/F ratio)) on admission were automatically abstracted from the electronic health record on the moment of admission. Laboratory assessment included hs-cTnT (Roche Diagnostics International Ltd.), NT-proBNP, C-reactive protein (CRP), ferritin and D-dimers. The first value upon admission was withheld when several blood samples were taken within one day. The cut-off for hs-cTnT was 14 pg/ml (corresponding with levels above the 99th percentile of a normal reference population) and for NT-proBNP 450 pg/mL.

During follow-up, the use of vasopressors, mechanical ventilation and/or venovenous extracorporeal membrane oxygenation was recorded. Transthoracic echocardiography was performed within the first 48 hours of inclusion, using a portable ultrasound machine CX50 (Philips Medical Systems, Andover, MA). The following parameters were evaluated: the global left ventricular (LV) function, left ventricular ejection fraction with eyeball-method (LVEF) (normal, midrange and reduced), LV end diastolic diameter (LVEDD), diastolic function (E/A ratio and E/e' septal), tricuspid annular plane systolic excursion (TAPSE), estimate systolic pulmonary arterial pressure (SPAP) using the maximal tricuspid regurgitation velocity with CW
Doppler, valvular function and presence of pericardial fluid. Diastolic function was dichotomized according to indices of diastolic dysfunction and increased left atrial pressure (E/A > 1.5 and/or E/e' septal > 14). Echocardiography was performed by six skilled sonographers, all images were stored in the Picture Archiving and Communication System (PACS) of the hospital. The primary outcome of the study was all-cause 30-day mortality.

Data analysis

The statistical analysis was performed using SPSS statistics (Version 27.0, IBM Corp, Armonk, NY). Normality of the distribution of continuous variables was tested by the Shapiro Wilk test. Categorical variables are shown as frequencies, and continuous variables as mean (standard deviation) or median (interquartile range) based upon normality of distribution. Comparison of categorical variables was performed using Chi-squared tests and for comparison of continuous variables Mann-Whitney U tests was used. Predictive markers for mortality were assessed by receiver operating characteristic (ROC) analysis and cut-off values by the Youden Index. The latter is a frequently used summary measure of the ROC curve. It represents the effectiveness of a diagnostic marker and enables the selection of an optimal threshold value (18). All tests were 2-sided with P < 0.05 considered statistically significant.

Results

Patient characteristics and outcomes

A total of 100 patients were included within 48 hours of ICU admission. Baseline characteristics are presented in Table 1. Median age was 63.5 years, and the population was predominantly male (66%). The mean body mass index (BMI) was 28.7 kg/m², 28% had type 2 diabetes mellitus and 42% was known with arterial hypertension. On admission the median total SOFA-score was 3.0, with a respiratory SOFA-score of 2.0. The median P/F-ratio on admission was 96.3 mmHg. The median length of stay in ICU was 10 days. Within the first 30 days after inclusion 21 patients died (21%). Non-survivors were significantly older and more often male. Respiratory SOFA, total SOFA and P/F ratio did not differ significantly between survivors and non-survivors.

Biomarkers

Biomarkers of inflammation (CRP, ferritin, D-dimer) did not differ significantly among survivors and non-survivors. Cardiac biomarkers were elevated in almost half of all included patients: hs-cTnT ≥ 14 pg/ml in 47%, and NT-proBNP ≥ 450 pg/ml in 39%. The level of these biomarkers was significantly higher in non-survivors (Table 2). Figure 1 shows a ROC-curve for all 5 biomarkers with their respective area under the curve (AUC). The biomarkers for inflammation were not associated with mortality, while the association of hs-cTnT (AUC: 0.79) and NT-proBNP (AUC: 0.71) was fair. Based on our data, we explored an optimal cut-off value for risk prediction for hs-cTnT and NT-proBNP. A value of 16.5 pg/ml for hs-cTnT corresponded with sensitivity and specificity for mortality of resp. 71.4 % and 48.6 %. The univariable odds ratio for 30-day all-cause mortality in patients with hs-cTnT ≥ 16.5 pg/ml was 8.5 (95% CI 2.9, 25.0).
For NT-proBNP, an optimal cut-off value of 415.5 pg/ml corresponded with sensitivity and specificity for mortality of resp. 71.4 % and 38.5 %. The univariable odds ratio for 30-day all-cause mortality in patients with NT-proBNP ≥ 415.5 pg/ml was 5.1 (95% CI 1.8, 14.7). Survival analysis curves are shown in Fig. 2. Unadjusted odds ratio's (OR) for 30-day all-cause mortality for cardiac biomarkers is in Fig. 3.

**Echocardiography**

Transthoracic echocardiography was not feasible in 11 patients (11%) due to poor visualization or prone ventilation. LVEF was reduced in 19.1% of patients (Table 1). LVEF was significantly lower in those who ultimately died (Table 2). Levels of hs-cTnT and NT-proBNP were elevated in up to respectively 38.9% and 34.7% of patients with normal LVEF. Right ventricular function, evaluated by TAPSE, was normal (> 14mm) in 94.8% of our cohort. After dichotomization between normal and abnormal TAPSE (≥ vs < 14 mm), patients with an abnormal RV function had higher mortality but this increase was not significant. There was no significant difference between survivors and non-survivors concerning diastolic function. The presence of moderate to severe valvular regurgitation (aortic, mitral, and tricuspid) or pericardial effusion did not differ significantly between the two groups. Unadjusted OR's for 30-day all-cause mortality for echocardiographic findings are shown in Fig. 3.

**Discussion**

This prospective study in critically ill COVID-19 patients has six important findings: (I) elevated levels of hs-cTnT and NT-proBNP upon admission are common and were found in respectively 47% and 39% of patients, (II) Elevated cardiac biomarkers are not necessarily linked to ventricular dysfunction as around 40% of patients with normal ejection fraction had either elevated levels of hs-cTnT and/or NT-proBNP, (III) Elevated levels of hs-cTnT, and to a lesser extent, NT-proBNP were associated with mortality, (IV) Serum levels of frequently used markers of inflammation (C-reactive protein, D-dimers and ferritin) and other clinical parameters of disease-severity (total SOFA, respiratory SOFA and P/F ratio) were not predictive for mortality, (V) Decreased LV function was associated with worse prognosis, whereas diastolic dysfunction and impaired RV function were not, (VI) cardiac ultrasound was not possible for various reasons in as much as 11% of this cohort of critical COVID-19 patients.

Whether cardiac biomarkers should be systematically measured as part of the workup for every hospitalized COVID-19 patient remains subject of debate. Currently, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) recommend against their routine use, while awaiting more evidence, as they warn for unnecessary diagnostic investigations, risk exposure and medical overuse (16, 17). Another reason to not currently recommend the routine use of cardiac biomarkers in prognostication is the belief that these markers would only be of limited incremental prognostic value to other markers of disease-severity (19), which is in contrast with the findings in our study and previous research. In an early report of 191 patients with COVID-19 in Wuhan, the univariable odds ratio for mortality when hs-cTnT was above the 99th percentile upper reference limit was 80.1 (95% CI, 10.3–620.4; P < 0.0001) regardless of underlying cardiovascular disease. This was higher than for all other biomarkers or scores tested, including D-dimers, ferritin and SOFA-score (20). Another study by Manocha
et al. showed that hs-cTnT was the only independent predictor of mortality among the same five biomarkers (i.e. CRP, ferritin, D-dimers, NT-proBNP and hs-cTnT), whereas Shi et al. found statistical significance for both hs-cTnT and NT-proBNP (21, 22). Our results are in line with these findings and support the statement of Sandoval et al. that the use of cardiac biomarkers for prognostic purposes may help in risk-stratification (23). We furthermore agree that this should not necessarily lead to unnecessary diagnostic testing when it is accompanied by clear education about the goals and implications of potentially elevated biomarkers (23).

We observed a reduced left and right ventricular function in respectively 17% and 5.2% of our patients. Previous large-scale research found similar results concerning reduced left ventricular function (20%), whereas right ventricular function was reduced in about 30% (10). Based on our data, reduced left ventricular systolic function was associated with mortality. However, right ventricular function, assessed with TAPSE, was not. Due to the low number of patients with reduced right ventricular contractility one should interpret this finding with caution. In previous research, left- and right ventricular function, analyzed with strain measurements, were both correlated with poor outcome (10, 14, 24). Diastolic dysfunction, based upon E/A and E/e' measurement, was not associated with higher odds for 30-day all-cause mortality. A prospective study of Szekely et al. showed similar results for E/A, though elevated E/e' in their cohort was associated with a higher hazard ratio for death. However, this result just narrowly met statistical significance (HR 1.08, 95% CI: 1.001, 1.2) (9). Overall, comparison of echocardiographic findings in COVID-19 subjects is difficult given the large heterogeneity in study populations and measurement approaches (24).

The fact that patients with elevated cardiac biomarkers did not necessarily have a reduced LVEF underlines the hypothesis that cardiac injury in COVID-19 may be due to a myriad of causes including direct myocardial injury of SARS-CoV-2 and indirect myocardial stress due to respiratory failure, thrombogenicity, sympathetic stimulation, cytokine release and endothelial dysfunction (19, 25, 26). As such, elevated cardiac biomarkers may represent disease severity in a more complete way than routine echocardiography. Moreover, routine echocardiography is not always possible in real-world practice due to practical (poor visualization and prone ventilation) or logistic problems, which limits its use even more. In the present cohort echocardiography was not feasible in about one tenth of patients. Furthermore, it exposes health care personnel to contagious risks and may be more time-consuming due to disinfection protocols. Taken together, the additive value of routine echocardiography on top of the measurement of cardiac biomarkers is questionable, even though reduced left ventricular function may predict worse outcome. This is in line with the ESC guidance, which currently recommends against performing echocardiography in COVID-19 patients, unless it is likely to alter the management strategy (16).

The current study has some important strengths. First, the study population was critically ill and prospectively evaluated, which contrasts with most studies evaluating all hospitalized patients retrospectively. Second, the combination of a prospective assessment of biomarkers and echocardiographic in the same study population is rather unique. To our knowledge, only two smaller similar series were previously published (27, 28). In these studies, LV dysfunction was common in
patients with elevated serum levels of hs-cTnT, though also present in 12% of patients without elevated levels of hs-cTnT (27, 28). However, possible relationships between the levels of cardiac biomarkers or echocardiographic findings and outcome parameters were not studied.

Five study limitations should also be addressed. First, no serial data of cardiac biomarkers was obtained, although this could be of interest as dynamic changes may add additive value in prognostication (23, 29). Second, extrapolation of these results should be done with caution as this was a single-center study in critical COVID-19 patients and criteria for admission to ICU may differ between hospitals. For instance, COVID-19 patients with mono-organ failure requiring high flow nasal cannula, as well as patients with established do-not-resuscitate orders were admitted to dedicated mid-care units and thus not included in the present study. Third, our study has a relatively small sample size and results must be validated in larger cohorts. Fourth, echocardiographic evaluation of LVEF was performed using eye-balling methodology and no strain-based measurements were obtained. Finally, the extent of preexisting cardiovascular disease was largely unknown and therefore no difference could be made between established cardiovascular disease and new COVID-19 induced cardiovascular abnormalities.

**Conclusion**

This study highlights the strong predictive value of the cardiac biomarkers hs-cTnT and NT-proBNP taken upon ICU admission in critically ill COVID-19 patients. They outperform other routinely used biomarkers, as well as clinical indices of disease severity in ICU in this specific cohort. Transthoracic echocardiography has several limitations and should therefore only be considered if it is likely to impact therapeutic management.

**Declarations**

**Ethics approval and consent to participate**

The study was approved by the local ethical committee (BC-07568, April 1\textsuperscript{st}, 2020).

**Consent for publication**

Informed consent of every patient or the legal representative was obtained prior to inclusion.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

N/A
Funding

N/A

Authors’ contributions

HS, SG and EH conceived the principal idea. BZ, SD, HS and SG performed the echocardiography. BZ and SD were major contributors in data analysis and writing the manuscript. EH was prime investigator of the project and was a major contributor in the data analysis. HS, SG and EH critically revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank Dr. Els Vandecasteele and Dr. Fiona Tromp for performing echocardiography in part of the patient population, as well as Daisy Vermeiren, Stephanie Bracke, Jolien Van Hecke and Anouska De Smeyster for the organization and logistic support during this project.

References

1. Anon. COVID-19 Map [Internet]. Johns Hopkins Coronavirus Resource Center. Available from: https://coronavirus.jhu.edu/map.html. Accessed 20 July 2021.

2. National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2021. Available from: https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed 3 June 2021.

3. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020 Jul;5(7):802–10.

4. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020 Mar;368:m1091.

5. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Jul;5(7):811–8.

6. Stefanini GG, Chiarito M, Ferrante G, Cannata F, Azzolini E, Viggiani G, et al. Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. Heart. 2020 Oct;106(19):1512–8.

7. Caro-Codón J, Rey JR, Buño A, Iniesta AM, Rosillo SO, Castrejon-Castrejon S, et al. Characterization of NT-proBNP in a large cohort of COVID-19 patients. Eur J Heart Fail. 2021 Mar;23(3):456–64.

8. Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, et al. Global evaluation of echocardiography in patients with COVID-19. Eur Hear journal Cardiovasc Imaging. 2020 Sep;21(9):949–58.
9. Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, et al. Spectrum of Cardiac Manifestations in COVID-19: A Systematic Echocardiographic Study. Circulation. 2020 Jul;142(4):342–53.

10. Karagodin I, Carvalho Singulane C, Woodward GM, Xie M, Tucay ES, Tude Rodrigues AC, et al. Echocardiographic Correlates of In-Hospital Death in Patients with Acute COVID-19 Infection: The World Alliance Societies of Echocardiography (WASE-COVID) Study. J Am Soc Echocardiogr. 2021 May;S0894-7317(21):00483–1.

11. Bansal A, Kumar A, Patel D, Puri R, Kalra A, Kapadia SR, et al. Meta-analysis Comparing Outcomes in Patients With and Without Cardiac Injury and Coronavirus Disease 2019 (COVID 19). Am J Cardiol. 2020 Nov;141:140–6.

12. Pranata R, Huang I, Lukito AA, Raharjo SB. Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: systematic review and meta-analysis. Postgrad Med J. 2020 Jul;96(1137):387–91.

13. Zhao B-C, Liu W-F, Lei S-H, Zhou B-W, Yang X, Huang T-Y, et al. Prevalence and prognostic value of elevated troponins in patients hospitalised for coronavirus disease 2019: a systematic review and meta-analysis. J intensive care. 2020 Nov;8(1):88.

14. Wibowo A, Pranata R, Astuti A, Tiksnadi BB, Martanto E, Martha JW, et al. Left and right ventricular longitudinal strains are associated with poor outcome in COVID-19: a systematic review and meta-analysis. J intensive care. 2021 Jan;9(1):9.

15. Li Y, Li H, Zhu S, Xie Y, Wang B, He L, et al. Prognostic Value of Right Ventricular Longitudinal Strain in Patients With COVID-19. JACC Cardiovasc Imaging. 2020 Nov;13(11):2287–99.

16. The European Society for Cardiology E. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. Available from: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESCCOVID-19-Guidance. Accessed 2 July 2021.

17. Januzzi J. Troponin, Use BNP. in COVID-19 [Internet]. American College of Cardiology. 2020. Available from: https://www.acc.org/latest-in-cardiology/articles/2020/03/18/15/25/troponin-and-bnp-use-in-covid19. Accessed 2 July 2021.

18. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. Biom J. 2005 Aug;47(4):458–72.

19. Mueller C, Giannitsis E, Jaffe AS, Huber K, Mair J, Cullen L, et al. Cardiovascular biomarkers in patients with COVID-19. Eur Hear journal Acute Cardiovasc care. 2021 May;10(3):310–9.

20. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar;395(10229):1054–62.

21. Manocha KK, Kirzner J, Ying X, Yeo I, Peltzer B, Ang B, et al. Troponin and Other Biomarker Levels and Outcomes Among Patients Hospitalized with COVID-19: Derivation and Validation of the HA(2)T(2) COVID-19 Mortality Risk Score. J Am Heart Assoc. 2020 Oct;e018477.
22. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J. 2020 Jun;41(22):2070–9.

23. Sandoval Y, Januzzi JL, Jaffe AS. Cardiac Troponin for Assessment of Myocardial Injury in COVID-19: JACC Review Topic of the Week. J Am Coll Cardiol [Internet]. 2020;76(10):1244–58.

24. Messina A, Sanfilippo F, Milani A, Calabrò L, Negri K, Monge García MI, et al. COVID-19-related echocardiographic patterns of cardiovascular dysfunction in critically ill patients: A systematic review of the current literature. J Crit Care. 2021 May;65:26–35.

25. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020 Jul;5(7):831–40.

26. Bader F, Manla Y, Atallah B, Starling RC. Heart failure and COVID-19. Heart Fail Rev. 2021 Jan;26(1):1–10.

27. Churchill TW, Bertrand PB, Bernard S, Namasivayam M, Churchill J, Crousillat D, et al. Echocardiographic Features of COVID-19 Illness and Association with Cardiac Biomarkers. J Am Soc Echocardiogr. 2020 Aug;33(8):1053–4.

28. Sud K, Vogel B, Bohra C, Garg V, Talebi S, Lerakis S, et al. Echocardiographic Findings in Patients with COVID-19 with Significant Myocardial Injury. J Am Soc Echocardiogr. 2020 Aug;33(8):1054–5.

29. Li C, Jiang J, Wang F, Zhou N, Veronese G, Moslehi JJ, et al. Longitudinal correlation of biomarkers of cardiac injury, inflammation, and coagulation to outcome in hospitalized COVID-19 patients. J Mol Cell Cardiol. 2020 Oct;147:74–87.

Tables

Table 1

Baseline demographics, disease severity, laboratory assessments and echocardiographic parameters of patients on admission to the intensive care unit.
| Demographics (n = 100) |
|------------------------|
| Age (y)                | 63.5 (IQR 57.0–71.0) |
| Gender                 |
| Male                   | 66 (66.0 %) |
| Female                 | 34 (34.0 %) |
| BMI (kg/m²)            | 28.7 (IQR 25.1–33.6) |
| Diabetes mellitus      | 28 (28.0 %) |
| Arterial hypertension  | 42 (42.0 %) |
| Severity of illness (n = 100) |
| Total SOFA-score on admission | 3.0 (IQR 2.0–8.0) |
| Respiratory SOFA-score on admission | 2.0 (IQR 2.0–3.0) |
| P/F ratio (IQR) on admission | 96.3 (IQR 71.6–124.7) |
| Use of vasopressors during admission | 54 (54.0 %) |
| Use of mechanical ventilation during admission | 60 (60.0 %) |
| Use of vv-ECMO during admission | 7 (7.0 %) |
| Inflammatory markers at time of inclusion (n = 100) |
| CRP (mg/L)             | 136.5 (IQR 67.0–201.3) |
| D-dimers (ng/mL)       | 1020.0 (IQR 660.0–1795.0) |
| Ferritin (µg/L)        | 1139.0 (IQR 640.8–2346.8) |
| Cardiac biomarkers at time of inclusion (n = 100) |
| hs-cTnT (µg/L)         |
| ≥ 14 µg/L              | 47 (47.0 %) |
| < 14 µg/L              | 53 (53.0 %) |
| NT-proBNP (pg/mL)      |
| ≥ 450 pg/mL            | 39 (39.0 %) |
| < 450 pg/mL            | 61 (61.0 %) |
| Echocardiography parameters at time of inclusion |
| LVEF (%) (n = 89)      |
| Normal (> 50%)         | 72 (80.9 %) |
### Table 2

| Demographics (n = 100) |  |
|------------------------|---|
| Midrange (40–50%)      | 16 (18.0 %) |
| Reduced (< 40%)        | 1 (1.1 %) |
| LVEDD (mm) (n = 83)    | 46.0 (IQR 43.0–51.0) |

**Diastolic function**

| E/A (n = 79) |  |
|-------------|---|
| < 1.5       | 85 (85.0 %) |
| ≥ 1.5       | 15 (15.0 %) |

| E/e’ septal (n = 72) |  |
|----------------------|---|
| < 14                | 60 (83.3 %) |
| ≥ 14                | 12 (16.7 %) |

**Right ventricular function**

| TAPSE > 14mm (n = 77) |  |
|------------------------|---|
| 73 (94.8 %)            |  |

| Pulmonary artery pressure (mmHg) (n = 51) |  |
|------------------------------------------|---|
| 24.0 (IQR 15.0–31.0)                    |  |

| Moderate to severe valvular dysfunction (n = 87) |  |
|-------------------------------------------------|---|
| 7 (8.0 %)                                        |  |

| Pericardial effusion (n = 89) |  |
|--------------------------------|---|
| 4.5 (4.5 %)                    |  |

*BMI*: body mass index. *vv-ECMO*: venovenous extracorporeal membrane oxygenation. *SOFa*: Sequential Organ Failure Assessment. *CRP*: c-reactive protein. *NT-proBNP*: N-terminal pro-brain natriuretic peptide. *hs-cTnT*: high sensitive troponin T. *LVEDD*: left ventricular end diastolic diameter. *DT*: deceleration time. *TAPSE*: tricuspid annular plane systolic excursion. *LVEF*: left ventricular ejection fraction. *MR*: mitral regurgitation. *AR*: aortic regurgitation. *TR*: tricuspid regurgitation. *ICU*: intensive care unit.

*Table 2*

*Distribution of baseline demographics, disease severity, laboratory assessments and echocardiographic parameters of patients between survivors and non-survivors.*
|                                | Survivors (n = 79) | Non-survivors (n = 21) | P-value |
|--------------------------------|--------------------|------------------------|---------|
| **Demographics**               |                    |                        |         |
| Age (y)                        | 61.0 (IQR 52.0–71.0)| 69.0 (IQR 66.5–72.0)   | 0.008   |
| **Gender**                     |                    |                        |         |
| Male                           | 48 (60.8 %)        | 18 (85.7 %)            | 0.032   |
| Female                         | 31 (39.2 %)        | 3 (14.3 %)             |         |
| **BMI (kg/m²)**                | 28.9 (IQR 25.7–33.9)| 25.8 (IQR 22.4–31.4)   | 0.034   |
| **Diabetes mellitus**          | 22 (27.8 %)        | 6 (28.6 %)             | 0.948   |
| **Arterial hypertension**      | 33 (41.8 %)        | 9 (42.9 %)             | 0.929   |
| **Length of stay ICU (d)**     | 10.0 (IQR 5.0–16.0)| 15.0 (IQR 6.5–24.0)    | 0.085   |
| **Severity of illness at time of inclusion** | | | |
| Use of vasopressors            | 36 (45.6 %)        | 18 (85.7 %)            | 0.001   |
| Use of mechanical ventilation  | 42 (53.2 %)        | 18 (85.7 %)            | 0.007   |
| Use of vv-ECMO                 | 4 (5.1 %)          | 3 (14.3 %)             | 0.141   |
| Total SOFA-score               | 3.0 (IQR 2.0–8.0)  | 4.0 (IQR 2.0–11.5)     | 0.342   |
| Respiratory SOFA-score         | 2.0 (IQR 2.0–3.0)  | 2.0 (IQR 2.0–3.0)      | 0.784   |
| **P/F ratio (IQR)**            | 96.3 (IQR 70.2–120.6)| 92.9 (IQR 74.5–153.5)  | 0.375   |

**Inflammatory markers at time of inclusion**

| Marker                  | Survivors (mg/L) | Non-survivors (mg/L) | P-value |
|-------------------------|------------------|----------------------|---------|
| CRP (mg/L)              | 137.1 (IQR 69.0–208.0) | 125.5 (IQR 56.5–200.5)  | 0.496   |
| D-dimers (ng/mL)        | 1025.0 (IQR 640.0–1740.0) | 965.0 (IQR 625.0–2885.0) | 0.912   |
| Ferritin (µg/L)         | 1079.0 (IQR 661.0–2271.0) | 1492.0 (IQR 603.0–3072.0) | 0.469   |

**Cardiac biomarkers at time of inclusion**

| Biomarker               | Survivors (%)     | Non-survivors (%)   | P-value |
|-------------------------|-------------------|---------------------|---------|
| hs-cTnT (µg/L)          |                   |                     |         |
| ≥ 16.5 µg/L             | 18 (22.8 %)       | 15 (71.4 %)         | < 0.001 |
| < 16.5 µg/L             | 61 (77.2 %)       | 6 (28.6 %)          |         |
| NT-proBNP (pg/mL)       |                   |                     |         |
### Survivors (n = 79)  
### Non-survivors (n = 21)  
### P-value

|              | Survivors | Non-survivors | P-value |
|--------------|-----------|---------------|---------|
| ≥ 415.5 pg/mL| 26 (32.9 %) | 15 (71.4 %)  | 0.001   |
| < 415.5 pg/mL| 53 (67.1 %) | 6 (28.6 %)   |         |

Echocardiography parameters at time of inclusion

|                          | Survivors | Non-survivors | P-value |
|--------------------------|-----------|---------------|---------|
| **LVEF (%)**             |           |               |         |
| Normal (> 50%)           | 62 (86.1 %) | 10 (58.8 %)  | 0.011   |
| Midrange (40–50%)        | 10 (13.9 %) | 6 (35.3 %)   |         |
| Reduced (< 40%)          | 0 (0.0 %)  | 1 (5.9 %)    |         |
| **LVEDD (mm)**           | 47.0 (IQR 43.0–51.0) | 46.0 (IQR 40.0–54.0) | 1.000   |

**Diastolic function**

|                          | Survivors | Non-survivors | P-value |
|--------------------------|-----------|---------------|---------|
| **E/A**                  |           |               |         |
| < 1.5                    | 55 (83.3 %) | 12 (92.3 %)  | 0.410   |
| ≥ 1.5                    | 11 (16.7 %) | 1 (7.7 %)    |         |

|                          | Survivors | Non-survivors | P-value |
|--------------------------|-----------|---------------|---------|
| **E/e’ septal**          |           |               |         |
| < 14                     | 52 (86.7 %) | 8 (66.7 %)   | 0.090   |
| ≥ 14                     | 8 (13.3 %)  | 4 (33.3 %)   |         |

**Right ventricular function**

|                          | Survivors | Non-survivors | P-value |
|--------------------------|-----------|---------------|---------|
| **TAPSE > 14mm**         | 62 (96.9 %) | 11 (84.6 %)  | 0.069   |
| Pulmonary artery pressure (mmHg) | 22.0 (IQR 11.8–30.0) | 29.0 (IQR 26.0–37.0) | 0.043   |
| Moderate to severe valvular dysfunction | 4 (5.6 %)  | 3 (18.8 %)   | 0.081   |
| Pericardial effusion     | 3 (4.2 %)  | 1 (5.9 %)    | 0.759   |

**BMIs**: body mass index. **vv-ECMO**: venovenous extracorporeal membrane oxygenation. **SOFA**: Sequential Organ Failure Assessment. **CRP**: c-reactive protein. **NT-proBNP**: N-terminal pro-brain natriuretic peptide. **hs-cTnT**: high sensitive troponin T. **LVEDD**: left ventricular end diastolic diameter. **TAPSE**: tricuspid annular plane systolic excursion. **LVEF**: left ventricular ejection fraction. **MR**: mitral regurgitation. **AR**: aortic regurgitation. **TR**: tricuspid regurgitation. **ICU**: intensive care unit.

**Figures**
Figure 1

Receiver operating characteristic curve Receiver operating characteristic (ROC) curves for five biochemical markers: high-sensitive troponin T (panel A), N-terminal pro-brain natriuretic peptide (panel B), C-reactive protein (panel C), D-dimers (panel D) and ferritin (panel E). hs-cTnT: high-sensitive troponin T. NT-proBNP: N-terminal pro-brain natriuretic peptide. Area under the curve (AUC) 95% confidence interval P-value hs-cTnT 0.797 0.687 – 0.907 < 0.001 NT-proBNP 0.732 0.594 – 0.870 0.001 CRP 0.451 0.309 – 0.594 0.496 D-dimers 0.508 0.349 – 0.668 0.912 Ferritin 0.552 0.406 – 0.697 0.469
Survival analysis based upon the level of hs-cTnT and NT-proBNP on admission to ICU Survival analysis based upon both levels of high sensitive troponin T (panel A) and N-terminal pro-brain natriuretic peptide (panel B) on admission to ICU. hs-cTnT: high-sensitive troponin T. NT-proBNP: N-terminal pro-brain natriuretic peptide.
Figure 3

Univariable odds ratio for 30-day all-cause mortality for cardiac biomarkers hs-cTnT and NT-proBNP as well as several echocardiographic measurements (reduced left ventricular ejection fraction (LVEF), increased E/e', increased E/A, decreased tricuspid annular plane systolic excursion (TAPSE), valvular dysfunction and pericardial fluid). Both elevated cardiac biomarkers above their respective cut-off value and a reduced LVEF had a significant higher odds ratios for 30-day all-cause mortality. NT-proBNP: N-terminal pro-brain natriuretic peptide. hs-cTnT: high sensitive troponin T. TAPSE: tricuspid annular plane systolic excursion. LVEF: left ventricular ejection fraction. OR: odds ratio.