Early Triage Echocardiography to Predict Outcomes in Patients Admitted With COVID-19 – A Multicenter Study

Daniel Peck, MD[1], Andrea Z. Beaton, MD[1], Maria Carmo P. Nunes, MD, PhD[2,3], Nicholas J. Ollberding, PhD[4,5], Allison G. Hays, MD[6], Pranoti Hiremath, MD[6], Federico M. Asch, MD[7], Nitin Malik, MD[7], Christopher Fung, MD[8], Craig A. Sable, MD[9], Bruno R Nascimento, MD, MSc, PhD, FACC, FESC[2,3]. *On behalf of the CV-19 investigators*.

[1] The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati - OH, United States; [2] Serviço de Cardiologia e Cirurgia Cardiovascular e Centro de Telessaúde do Hospital das Clínicas da UFMG, Belo Horizonte - MG, Brazil; [3] Faculdade de Medicina da Universidade Federal de Minas Gerais, Belo Horizonte - MG, Brazil; [4] Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [5] Department of Pediatrics, University of Cincinnati, Cincinnati, OH, USA [6] Cardiology, The Johns Hopkins Hospital, Baltimore – MD, United States; [7] MedStar Washington Hospital Center and MedStar Health Research Institute, Washington - DC, Unites States; [8] Cardiovascular Center, University of Michigan Hospital, Ann Harbor – MI, United States; [9] Cardiology, Children's National Health System, Washington – DC, United States

This study was funded by the American Heart Association Award #810968, USA, and by FAPEMIG (Fundação de Amparo à Pesquisa do Estado de Minas Gerais, grant #APQ-000627-20), Brazil and received in-kind technological support from Trice Imaging.

The funder did not have any relationship with the conduct of the study, data collection, analysis, and interpretation, and the preparation, review, or approval of this manuscript.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/echo.15567.

Corresponding author: Prof. B. R. Nascimento, MD, MSc, Ph.D, FACC, FESC

Serviço de Cardiologia e Cirurgia Cardiovascular

Hospital das Clínicas da Universidade Federal de Minas Gerais

Rua Muzambinho, 710, apt. 802, Serra, Belo Horizonte, Minas Gerais, Brasil, CEP 30.210-530

E-mail: ramosnas@gmail.com

Word-count: 3,548 words.

Abstract:

Introduction: Cardiac involvement seems to impact prognosis of COVID-19, especially in critically ill patients. We aimed to assess the prognostic value of right ventricular (RV) and left ventricular (LV) dysfunction, evaluated by bedside triage echocardiography (echo), in patients admitted to emergency departments (ED) in the US with COVID-19. We also assessed the feasibility of using cloud imaging for sharing and interpreting echocardiograms.

Methods: Patients admitted to three reference EDs with confirmed COVID-19 underwent triage echo within 72h of symptom onset with remote interpretation. Clinical and laboratory data, as well as COVID-19 symptoms, were collected. The association between echo variables, demographics and clinical data with all-cause hospital mortality and intensive care unit (ICU) admission was assessed using logistic regression.

Results: 399 patients were enrolled, 41% women, with a mean age of 62±16 years. Mean oxygen saturation on presentation was 92.3± 9.2%. Compared to in-hospital survivors, non-survivors were older, had lower oxygen saturation on presentation, were more likely to have a chronic condition and had lower LV ejection fraction (50.3±19.7% vs. 58.0±13.6%) (p<0.05). In the cohort, 101 (25%) patients had moderate/severe LV dysfunction, 131 (33%) had moderate/severe RV dysfunction. Advanced age and lower oxygen saturation were independently associated with death and ICU admission. LV and RV function, or other echo variables, were not independent predictors of outcomes.

Conclusion: In patients admitted with COVID-19 undergoing early echo triage, the independent predictors of death and ICU admission were age and oxygen saturation. The inclusion of echo variables did not improve prediction of unfavorable outcomes.

Key-words: COVID-19; echocardiography; triage; outcomes; mortality.

Introduction:

The coronavirus disease 19 (COVID-19) pandemic, caused by widespread infection with severe acute respiratory syndrome coronavirus (SARS-CoV-2), has resulted in an unprecedented

number of patients presenting acutely ill to emergency departments (EDs). Such an overwhelming influx of ill patients has highlighted the importance of efficient, accurate assessment and triage to identify high-risk patients. To address this challenge, numerous COVID-19 risk prediction models have been developed that incorporate patient demographics (e.g., gender, age), comorbidities (e.g., hypertension, diabetes, obesity) and clinical data (e.g., vitals, laboratory vitals) to predict mortality and ICU admission.[1–3] While these models include most predictive variables, many lack a thorough assessment of cardiac function beyond a troponin value.

Several studies have demonstrated that COVID-19, in addition to the obvious pulmonary manifestations, has significant deleterious effects on cardiac function. COVID-19 infection affects the cardiovascular system through multiple pathways, including direct injury of myocardial cells by the infecting virus, the negative effects associated with the inflammatory response, plaque rupture and thrombosis, and impaired pulmonary vasoreactivity leading to right heart strain.[4–7] The combination of these insults results in a various degrees of cardiovascular dysfunction, most notably right ventricular (RV) dysfunction, elevated pulmonary pressure, and to a lesser extent, left ventricular (LV) dysfunction.[8] Further, the development of cardiac dysfunction has been shown to be independently associated with mortality.[9,10]

Given the association between COVID-19 infection and cardiovascular dysfunction leading to poor outcomes, an early assessment with bedside echocardiogram on initial presentation could enable identification of these patients sooner, thus optimizing patient care. While not intended to be a comprehensive evaluation, point of care echocardiography in the EDs can provide valuable information about biventricular function, pericardial effusions, valve disease, and myocardial ischemia.[11–15] Point of care echocardiography can be particularly useful in resource limited settings where specialized services are scarce. Focused exams have been successfully utilized for rheumatic heart disease diagnosis and for the assessment of critically ill patients in low resource settings.[16,17] Such information may prove very useful to determine the appropriate triage and likely trajectory for patients presenting with acute COVID-19 infection.

The purpose of this study was to evaluate whether focused assessment with point of care echocardiography within 72 hours of presentation improved the prediction of death or ICU admission in patients presenting with COVID-19 to the ED, when compared to a model comprised of a minimal set of readily available clinical variables. In addition, we assessed the feasibility of implementing a variety of focused echo protocols in the ED and sharing heterogeneous image files via a single cloud server for storage, interpretation, and research during the pandemic.

Methods:

This was a multi-center retrospective cohort study. Data were collected in 3 enrolling sites: University of Michigan (Ann Harbor, MI, US), MedStar Washington Hospital Center (Washington, DC, US) and Johns Hopkins (Baltimore, MD, US). Adult patients aged 18 years and older with confirmed COVID-19 infection who had an echocardiogram within the first 72 hours of presentation, at the discretion of the attending staff, were included in the study. Echocardiograms were obtained per individual hospital protocols for clinical purposes, with clinically validated standard or portable/handheld devices, by physicians and/or trained sonographers. All providers who acquired echocardiograms were at a minimum certified for pocket ultrasound / echocardiography, or supervised by certified personnel. Most of the images were acquired by cardiologists or cardiology fellows. Participating institutions performed a retrospective search of their echocardiographic database and electronic medical record to identify patients who had a confirmed diagnosis of COVID-19 infection and an echocardiogram obtained within the first 72 hours of presentation. Consecutive or random inclusion of patients was left to the discretion of each institution, as a convenience sampling. Medical record review was performed to extract demographic, clinical and echocardiographic data. Clinical data included pulse oximetry, clinical comorbidities (hypertension, type 2 diabetes, heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease, cerebrovascular disease), Emergency Severity Index, duration of COVID-19 and systemic and

respiratory symptoms reported. All data were collected from medical records, informed at patient admission.

Deidentified echocardiograms (both DICOM and non-DICOM) were uploaded to a secure cloud server (Trice®, Imaging Del Mar California), compliant with the Health Insurance Portability and Accountability Act (HIPAA) and certified for electronic protected health information, and underwent expert blinded review by cardiologists in the United States and Brazil. Reviewers could securely review images and make measurements using the cloud platform or choose to accept existing measurements that were included in still frames as part of each study. Qualitative and quantitative variables were recorded following the post-hoc consensus analyses of images. Echocardiographic data recorded for the study included assessment of biventricular size and function, valvar stenosis or regurgitation, left atrial size, presence of pericardial effusion, tricuspid regurgitant (TR) jet velocity, tricuspid valve annular plane systolic excursion (TAPSE), tissue Doppler imaging (TDI), and mitral inflow velocities. LV function was graded as normal or mildly, moderately or severely depressed based on left ventricular ejection fraction (LVEF) per guideline recommendations, or qualitatively graded and RV function was only qualitatively graded.[18] Valvar regurgitation was graded as absent, mild, moderate, or severe and pericardial effusions were similarly categorized as absent, small, moderate or large.[19,20] Institutions were divided into "high" or "low" imaging resource centers, based on echo resources at the EDs, in order to determine if triage echo had a greater benefit in either setting: in low-resource centers a focused echo protocol was applied, including qualitative assessment of biventricular size and function, valvar function, and the presence of pericardial effusion, whereas in higher-resource units a comprehensive protocol with quantitative assessment was utilized.

The primary end point of the study was in-hospital mortality, and the secondary endpoint was ICU admission. All demographic, clinical, and echocardiographic variables were evaluated using

bivariate and multivariable analysis to determine correlation with the primary and secondary endpoints.

Statistical analysis:

Patient demographic and clinical characteristics were described using means with standard deviations (SD) and numbers and percentages. Differences in demographic and clinical characteristics according to in-hospital mortality were tested using two-sample sample t-tests and chi-square tests for independence. In addition, relevant clinical variables were compared between individuals with and without left and right ventricular dysfunction (moderate and severe). Logistic regression was used to obtain odds ratios and predicated probabilities for in-hospital mortality and ICU admission. A minimal clinical model, including data from both high and low-resource EDs, was first fit that included age, sex, count of co-morbid conditions, and pulse oximetry as covariates and selected based on a review of published COVID-19 prediction models.[3] Echocardiogram measurements were added to the clinical model to assess their contribution to predictive performance. Echocardiographic variables included severity of LV dysfunction, RV dysfunction, and pericardial effusion (none/mild vs. moderate/severe). Secondary models were fit to data for those sites that collected quantitative echocardiographic measurements to assess LV systolic and diastolic function, RV function and pulmonary artery pressure, including: LVEF, mitral inflow to lateral TDI ratio, TR velocity, and TAPSE. Age and quantitative echocardiogram measures were modeled using restricted cubic spline terms with three degrees of freedom (d.f.; knots at 10^{th}, 50^{th}, and 90^{th} percentiles) to capture potential non-linear associations. Measure of model performance included Akaike's information criterion (AIC); optimism corrected estimates for the R^2, c-statistic, Brier score, calibration intercept and slope; and a likelihood ratio test (LRT) of nested models. Corrected estimates and calibration curves were obtained using bootstrap resampling (n=500 resamples). Missing data were observed for LVEF (n=54), mitral inflow to lateral TDI ratio (n=95), TR velocity (n=129), and TAPSE (n=67) patients among the 262 eligible for those measurements. Multiple

imputation with predictive mean matching was used to impute missing values (n=50 datasets). Imputation models included all variables included in the analysis models, as well as race, ethnicity, body mass index, hypertension, heart failure, presence of type 2 diabetes, chronic kidney disease, and presence of other chronic health conditions (yes/no) as auxiliary variables to extend the missing at random assumption. Optimism corrected estimates of performance for models requiring imputation were obtained by pooling the values across all 50 datasets and reporting the mean (minimum, maximum) values. All analyses were conducted using the R software environment for statistical computing and graphics.[21] Model fitting, validation, and calibration were performed using the rms package.[22] Multiple imputation was performed using the aregImpute function in the Hmisc package.[23]

Results:

Patient Data

From April 2020 to, April 2021 (12 months), 399 patients (University of Michigan N=137, MedStar Washington Hospital Center: N=72 and Johns Hopkins N=190) presenting to the EDs with acute COVID-19 infections underwent echocardiogram within 72 hours of presentation. Of these, 137 (34%) were acquired with portable/handheld devices. Baseline clinical and demographic data are presented in **Table 1**. The mean age of patients was 62±16 years and 41% were female. The mean oxygen saturation on presentation was 92.3±9.2%. Comorbidities were present in 256 (64%), and the average number of comorbidities in the cohort was 2.1±1.7. Data about COVID-19 symptoms at presentation are depicted the **Supplement Table 1**. Comparing non-survivors and survivors, the non-survivors were older, had lower oxygen saturation and worse Emergency Severity Index at presentation, were more likely to have a chronic condition and less likely to present with muscle pain (p<0.05).

Echocardiographic Findings

All echocardiographic images, with different file formats (DICOM, Mpeg4 and other native video formats) could be consistently shared through the same cloud system (Trice Imaging, Del Mar, California) throughout the study, allowing for adequate remote interpretation in Brazil (MCN) and the US (SC). The same online system was successfully utilized to perform quantitative analyses of DICOM images, including advanced measurements, and semi-quantitative and qualitative analyses of non-DICOM files. No clinically relevant technical issues were reported.

The results from the focused echocardiograms are also shown in **Table 1**. In the entire cohort, 101 (25%) patients had moderate or severe LV dysfunction, 131 (33%) had moderate or severe RV dysfunction, and 9 (2%) had a moderate or large pericardial effusion. The average LVEF for the overall cohort was 56.3±15.4%. Non-survivors had a lower average LVEF than survivors at presentation (58.0±13.5 vs. 50.3±19.7, p<0.01). There were no other statistically significant differences in echocardiogram findings on bivariate analysis between survivors and non-survivors. When comparing individuals with and without moderate to severe ventricular dysfunction, those with significant RV involvement had a higher prevalence of COPD (**Supplement Table 2**).

Patient and Echocardiogram findings associated with in-hospital mortality

The contribution of echocardiogram findings to the prediction of in-hospital mortality is provided in **Table 2**. For the minimal clinical model comprised of age, sex, count of co-morbid conditions, and oxygen saturation, measures of model performance included R^2=0.1, c-statistic=0.68, and Brier score=0.14. Inclusion of severity of LV dysfunction, RV dysfunction, and pericardial effusion were not found to improve model performance (R^2=0.08, c-statistic=0.67, and Brier score=0.15, LRT p=0.67). Similarly, LVEF, mitral inflow to lateral TDI ratio, TR velocity, and TAPSE were not found to improve model performance over the clinical model in the subset of eligible patients from high-resource centers (R^2=0.06, c-statistic=0.66, and Brier score=0.17, LRT p=0.19). Calibration curves of predicted values were not improved with the inclusion of echocardiogram **(Supplement Figure 1)**. Odds ratios for in-hospital mortality according to clinical predictors and echocardiographic findings are provided in **Table 3**. Advanced age and lower oxygen saturation on presentation were associated

with in-hospital mortality, but LV dysfunction, RV dysfunction, or presence of a pericardial effusion were not. The predicted probabilities for in-hospital mortality according to continuous echocardiographic findings are presented in **Figure 1**.

Echocardiographic characteristics associated with ICU admission

Odds ratios for patient and echocardiogram findings associated with ICU admission are demonstrated in **Table 4**. Advanced age and lower oxygen saturation on presentation were again the only variables associated with ICU admission. Echocardiogram findings were not found to improve the prediction of ICU admission over the minimal set of clinical predictors (data not shown).

Discussion:

These prospective data, derived from 399 COVID-19 patients undergoing point-of-care echocardiography, showed that variables derived from simplified echocardiographic protocols did not add to the performance of predictive models for mortality or ICU admission when compared to a minimal set of readily available clinical variables. Although LVEF tended to be lower in individuals with unfavorable outcomes, age and oxygen saturation were the only independent predictors of death and need for intensive care.

The role of cardiac disease in COVID-19 remains unclear. Although there is compelling data about cardiac involvement by the disease, the time of its onset on disease course, associated factors, predictors and determinants still require investigation. The pathophysiology of cardiovascular disease includes viral invasion leading to direct myocardial injury, systemic inflammatory response and cytokine storm resulting in multiple-organ lesions, plaque rupture and thrombosis, and increased cardiometabolic demand in a scenario of worsening cardiac function.[4–6] In addition, involvement of the pulmonary circulation and impaired vascular reactivity also increase the risk of right heart overload and pulmonary hypertension.[7] Thus, there has been much interest in identifying cardiac involvement in the early phases of COVID-19, to guide intensive care and monitoring for

these patients. Considering its practicality and ease-to-use at bedside, point-of-care echocardiography has been the method of choice for this purpose in multiple studies.[9,10,24]

Since the inception of the COVID-19 pandemic, efforts have been made to develop models to predict unfavorable outcomes, combining clinical variables and complementary tests, including imaging. As in our study, the groups of variables most commonly included are demographics, clinical comorbidities, vital signs, image features, sex, lymphocyte count, and inflammatory markers. Among these, the ones most strongly associated with worse outcomes include age, D-dimer, C-reactive protein, lactate dehydrogenase, cardiovascular comorbidities and indicators of disease severity – noticeably oxygen saturation – one of the strongest predictors in this analysis.[3,25,26] The weight of such predictors – given their relevance in disease course – is frequently strong enough to outweigh other complementary tests, such as cardiac imaging. Predictive models, with a wide range of C-statistics and accuracy measures, are quickly moving from COVID-19 medical literature to clinical practice. However, they are prone to high risk of bias, in part due to the intrinsic heterogeneity of this new disease, and also due to overfitting of existing models.[3]

Considering this, the interest surrounding echocardiographic triage emerged since the first reports of cardiac involvement in COVID-19.[27] Despite the myriad of predictors of poor outcomes proposed, doubts still remain if abnormal findings indicate exacerbation of preexisting cardiac disease by COVID-19 or new structural/functional abnormalities induced by the infection. This question remains unanswered even by studies with advanced imaging.[28,29] In the largest echocardiographic studies, a large proportion of patients with COVID-19, and especially those hospitalized, had abnormal functional and structural findings, noticeably RV involvement (around 30% of the cases), elevated pulmonary pressure and LV impairment (in around 20%). Some publications, however, suggest a relative sparing of the LV, sometimes with a relatively reduced function in more severely ill patients, in accordance with our findings.[7,30] Some of these variables have been shown to predict adverse outcomes even after adjustment for clinical data, but the striking differences between study populations, in terms of severity, disease course and timing of

echo triage, limit definite conclusions. Considering this, a deeper analysis of our sampling and inclusion strategy provide some explanations for our results.[9,10] The COVID-19 sample consisted of patients seen at EDs, mostly in the early phases of infection. At this stage, new echo abnormalities may not have developed, and the slight differences in terms of LV systolic function between survivors and non-survivors may be more related to underlying cardiac disease. Of note, the only clinical comorbidity that distinguished patients with and without RV involvement was COPD, a known cause of pulmonary hypertension. Despite the lower severity at enrollment, the overall outcomes rates proved to be high (death in 19% and intensive care admission in 52% of patients) as in other echocardiographic studies.[9,10] The marked differences of age and oxygen saturation between survivors and those who perished, in addition to the timing of the echocardiography triage and choice of screening protocol, may have excluded other variables (such as ventricular function) from the model.

The triage protocol applied by the COVID-19 study was simplified and designed for fast-track application at bedside, and less-resourced institutions were allowed to utilize limited qualitative / semi-quantitative analyses with portable or even handheld devices. This precludes the exploration of variables that could more accurately evaluate ventricular involvement, as tissue Doppler and strain, found to predict outcomes in previous studies, as well as the permanence of echocardiography features in multivariable models. However the focus of this study is to leverage the practicality of echo triage, following the recommendation of level-1 protocols, for reducing contamination during the pandemic and allowing for more simplified training of non-experts, limited patient and scanner exposure and lower associated costs – in terms of devices, storage and even file sharing for remote interpretation.[5,27,31] The ability to upload both DICOM and non-DICOM echocardiograms from a variety of ultrasound machines to a single dedicated and secure, HIPPA compliant cloud server that provides ready access to cardiologists around the globe for image review and online measurements is an important innovation for both clinical care and research. Leveraging technology that has built-in IT security safeguards, does not require direct sharing of large image files, and allows access for

end users without downloading local client-based software, and provides measurement and reporting tools made this study feasible. While the pandemic drove increased utilization and advancement of this technology, it is now a mainstay of the global cardiology community.

Despite the lack of independent echocardiographic predictors of in-hospital outcomes, one of the key strengths of our study was to reinforce the feasibility and utility of fast-track echo triage for COVID-19 patients. More than identifying indicators of unfavorable outcomes at admission, the investigations of this technique may allow for: a) differential diagnoses, as several manifestations of COVID-19 overlap with those of cardiac diseases; b) easy and practical longitudinal assessment of cardiac function; c) fast identification of acute complications when worsening clinical parameters are observed; d) evaluation of cardiac and pulmonary sequelae in the long term, especially for individuals with persisting symptoms. Furthermore, our findings reinforce the importance of a targeted clinical triage, especially in terms of stratification by age, number of coexisting comorbidities and hypoxia parameters. Its usefulness may be better demonstrated in settings with scarce health resources, in the absence of adequate laboratory data and other complementary tests.

Limitations:

Our study has several limitations, mainly related to sample size and the timing of image acquisition in the COVID-19 clinical history. At first, enrolling institutions had different backgrounds in terms of complexity and access to advanced imaging. Thus, part of the sample included only limited screening protocols, without detailed quantitative variables and measurements, acquired by providers with limited and heterogeneous training backgrounds. This underpowers (i.e., may lead to overfitting) of the analysis of variables associated with worse prognosis in published studies, such as those associated with left and RV function and size, and dynamics of the pulmonary circulation. Second, in contrast to previous studies, we analyzed data from patients screened immediately following admission, most of them likely before the onset of severe inflammation / cytokine storm

and cardiac involvement, presumably limiting the accuracy of echo findings to predict outcomes. This may partially explain the differences between our observations and the existing literature, especially the lack of strong echocardiographic predictors.[9,32] Third, exams were acquired in a fixed time point (cross sectional analysis), and the longitudinal progression/regression of cardiac abnormalities during COVID-19 was not assessed. A follow-up study could provide additional insights about the long-term evolution of cardiac involvement in COVID-19. Fourth, ED staff may have screened patients with worse clinical status and higher chance of cardiac involvement, which would incur the risk of selection bias and decrease the models' ability to assess echo as a risk predictor. Furthermore, even in low-resource settings, all clinical and laboratory data was available to treating physicians: if only individuals with very limited data underwent echo triage, its role to independently predict risk in resource-limited scenarios could be better assessed. Finally, data collection was pragmatic – as the protocol was designed for application at bedside in COVID-19 units – and non-mandatory. As a result, further detailing of clinical variables may be lacking, as well as standardized laboratory data, and some missing data was observed. Noticeably, the heterogeneous degree of pulmonary involvement, based on imaging tests, was not available, nor detailed data on the phenotypic expression of COVID-19 was available. Information about the underlying cause of death (e.g. cardiac vs. non-cardiac) was not collected from death certificates either. Despite these limitations, to the best of our knowledge this was one of the largest pooled analyses of multicenter echocardiographic data derived COVID-19 patients at the point-of-care in the Americas, and our findings may add to the developing literature about the predictors of adverse outcomes, noticeably in the early phases of the disease.

Conclusion:

In this subset of patients admitted with COVID-19 and undergoing triage echo within 72 hours of symptom onset, the independent predictors of unfavorable outcomes (death and ICU

admission) were age and oxygen saturation. Despite the differences in baseline LVEF, no echo variables were independently associated with unfavorable outcomes, and clinical predictive models were not improved by their addition. The implementation of screening echo in the emergency setting for COVID-19 patients with cloud sharing of images for remote interpretation seem to be technically feasible. Additional investigations are warranted to better establish its role for risk-stratification in different scenarios and disease stages, especially when additional tests are scarce.

Conflicts of interest:

The authors have no relevant conflicts of interest related to this study.

Data availability statement:

Data analytic methods and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure, from the corresponding author upon reasonable request.

Funding:

The American Heart Association, CV-19 Rapid Response Grant (810968). Trice - Cloud Medical Imaging allowed the CV-19 program to utilize the dedicated cloud services in-kind, provided training on the utilization of systems for sharing and reading echocardiographic images, and provided de-identification of the exams. Dr Nascimento is partially financed by CNPq (Bolsa de produtividade em pesquisa, 312382/2019-7), by the Edwards Lifesciences Foundation (Improving the Prevention and Detection of Heart Valve Disease Across the Lifespan, 2021) and by FAPEMIG (grant APQ-000627-20). Medical students received scholarships from the National Institute of Science and Technology for Health Technology Assessment (IATS, project: 465518/2014-1).

Authors' Contributions:

Daniel Peck: Investigation, Methodology, Writing - original draft, Writing - review & editing; Andrea Z. Beaton: Conceptualization, Data curation, Funding acquisition, Investigation, Supervision, Project Administration; Maria Carmo P. Nunes: Investigation, Data curation; Nicholas J. Ollberding: Formal analysis; Allison Hays: Investigation; Pranoti Hiremath: Investigation; Federico Asch: Investigation; Nitin Malik: Investigation; Christopher Fung: Investigation; Laurie LeBouef: Investigation; Craig A. Sable: Conceptualization, Funding acquisition, Investigation, Software, Supervision, Writing - review & editing; Bruno R Nascimento: Investigation, Supervision, Roles/Writing - original draft, Writing - review & editing.

References:

1. Shakeel SM, Kumar NS, Madalli PP, Srinivasaiah R, Swamy DR. Covid-19 prediction models: A systematic literature review. *Osong Public Heal Res Perspect*. 2021;12(4):215-229. doi:10.24171/J.PHRP.2021.0100

2. Locquet M, Diep AN, Beaudart C, et al. A systematic review of prediction models to diagnose COVID-19 in adults admitted to healthcare centers. *Arch Public Heal*. 2021;79(1):1-15. doi:10.1186/s13690-021-00630-3

3. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ*. 2020;369:m1328. doi:10.1136/bmj.m1328

4. Bansal M. Cardiovascular disease and COVID-19. *Diabetes Metab Syndr Clin Res Rev*. 2020;14(3):247-250. doi:10.1016/j.dsx.2020.03.013

5. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109(5):531-538. doi:10.1007/s00392-020-01626-9

6. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med*. 2020;58(7):1131-1134. doi:10.1515/cclm-2020-0198

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(1):91-100. doi:10.1016/j.cjco.2020.09.016

8. Jones criteria (revised) for guidance in the diagnosis of rheumatic fever. *Circulation*. 1965;32(4):664-668. doi:10.1161/01.cir.13.4.617

9. Pimentel SLG, Nascimento BR, Franco J, et al. Bedside echocardiography to predict mortality of COVID-19 patients beyond clinical data: Data from the PROVAR-COVID study. *Rev Soc Bras*

Med Trop. 2021;54(January):1-9. doi:10.1590/0037-8682-0382-2021

10. Michelle D. Gomez J, Zimmerman AC, du Fay de Lavallaz J, et al. Echocardiographic Predictors of Mortality and Morbidity in COVID-19 Disease Using Focused Cardiovascular Ultrasound. *IJC Hear Vasc*. 2022;39:100982. doi:10.1016/j.ijcha.2022.100982

11. Kimura BJ, Yogo N, O'Connell CW, Phan JN, Showalter BK, Wolfson T. Cardiopulmonary limited ultrasound examination for "quick-look" bedside application. *Am J Cardiol*. 2011;108(4):586-590. doi:10.1016/j.amjcard.2011.03.091

12. Randazzo MR, Snoey ER, Levitt MA, Binder K. Accuracy of emergency physician assessment of left ventricular ejection fraction and central venous pressure using echocardiography. *Acad Emerg Med*. 2003;10(9):973-977. doi:10.1197/S1069-6563(03)00317-8

13. Mandavia DP, Hoffner RJ, Mahaney K, Henderson SO. Bedside echocardiography by emergency physicians. *Ann Emerg Med*. 2001;38(4 SUPPL.):377-382. doi:10.1067/mem.2001.118224

14. Thomas F, Flint N, Setareh-Shenas S, Rader F, Kobal SL, Siegel RJ. Accuracy and Efficacy of Hand-Held Echocardiography in Diagnosing Valve Disease: A Systematic Review. *Am J Med*. 2018;131(10):1155-1160. doi:10.1016/j.amjmed.2018.04.043

15. Moore CL, Rose GA, Tayal VS, Sullivan M, Arrowood JA, Kline JA. Determination of Left Ventricular Function by Emergency Physician Echocardiography of Hypotensive Patients. *Acad Emerg Med*. 2002;9(3):186-193. doi:doi: 10.1111/j.1553-2712.2002.tb00242.x.

16. Becker TK, Tafoya CA, Osei-Ampofo M, et al. Cardiopulmonary ultrasound for critically ill adults improves diagnostic accuracy in a resource-limited setting: the AFRICA trial. *Trop Med Int Heal*. 2017;22(12):1599-1608. doi:10.1111/tmi.12992

17. Beaton A, Aliku T, Okello E, et al. The utility of handheld echocardiography for early diagnosis

of rheumatic heart disease. *J Am Soc Echocardiogr*. 2014;27(1):42-49. doi:10.1016/j.echo.2013.09.013

18. Lang RM, Badano LP, Victor MA, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39.e14. doi:10.1016/j.echo.2014.10.003

19. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30(4):303-371. doi:10.1016/j.echo.2017.01.007

20. DeMaria DM, Waring AA, Gregg DE, Litwin SE. Echocardiographic Assessment of Pericardial Effusion Size: Time for a Quantitative Approach. *J Am Soc Echocardiogr*. 2019;32(12):1615-1617.e1. doi:10.1016/j.echo.2019.08.019

21. R Core Team. No Title. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Published 2021. https://www.r-project.org/

22. Harrell Jr FE. No Title. rms: Regression Modeling Strategies. R package version 6.2-0. Published 2021. https://cran.r-project.org/package=rms

23. Harrell Jr FE. No Title. Hmisc: Harrell Miscellaneous. R package version 4.6-0.

24. Zhang L, Wang B, Zhou J, Kirkpatrick J, Xie M, Johri AM. Bedside Focused Cardiac Ultrasound in COVID-19 from the Wuhan Epicenter : The Role of Cardiac Point-of-Care Ultrasound , Limited Transthoracic Echocardiography , and Critical Care Echocardiography. *J Am Soc Echocardiogr*. 2020;33(6):676-682.

25. Galanter W, Rodríguez-Fernández JM, Chow K, et al. Predicting clinical outcomes among

hospitalized COVID-19 patients using both local and published models. *BMC Med Inform Decis Mak*. 2021;21(1):1-18. doi:10.1186/s12911-021-01576-w

26. Maestrini V, Birtolo LI, Francone M, et al. Cardiac involvement in consecutive unselected hospitalized COVID-19 population: In-hospital evaluation and one-year follow-up. *Int J Cardiol*. 2021;339:235-242. doi:10.1016/j.ijcard.2021.06.056

27. Lassen MCH, Skaarup KG, Lind JN, et al. Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. *ESC Hear Fail*. 2020;7(6):4189-4197. doi:10.1002/ehf2.13044

28. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. *J Cardiovasc Electrophysiol*. 2020;31(5):1003-1008. doi:10.1111/jce.14479

29. Nascimento BR, Sable C. Cardiac involvement in COVID-19: cause or consequence of severe manifestations? *Heart*. 2022;108(1):7-8. doi:10.1136/heartjnl-2021-320246

30. Li Y, Li H, Zhu S, Xie Y, Wang B, He L. Prognostic value of right ventricular longitudinal strain in patients with COVID-19. *JACC Cardiovasc Imaging*. 2020;13(11):2287-2299.

31. Chamsi-Pasha MA, Sengupta PP, Zoghbi WA. Handheld Echocardiography: Current State and Future Perspectives. *Circulation*. 2017;136(22):2178-2188. doi:10.1161/CIRCULATIONAHA.117.026622

32. Scudiero F, Silverio A, Muraca I, et al. Long-Term Prognostic Impact of Right Ventricular Dysfunction in Patients with COVID-19. *J Pers Med*. 2022;12(2):1-10. doi:10.3390/jpm12020162

Tables:

Table 1: Participant demographic and clinical characteristics according to in-hospital mortality.

Variable:	**Survived = 323**	**Died = 76**	**p-value**
Age, mean (SD)	60.61 (16.67)	68.22 (11.81)	**<0.01**
Male, n (%)	191 (59.1)	44 (57.9)	0.95
Race, n (%)			0.75
Black	138 (43.1)	36 (48.0)	
Other	60 (18.8)	13 (17.3)	
White	122 (38.1)	26 (34.7)	
Non-Hispanic, n (%)	267 (86.1)	64 (85.3)	0.99
Body mass index, mean (SD)	31.13 (9.00)	29.09 (6.96)	0.07
Hypertension, n (%)	176 (54.5)	41 (53.9)	0.99
Heart failure, n (%)	42 (13.0)	14 (18.4)	0.30
Type 2 diabetes, n (%)	99 (30.7)	29 (38.2)	0.26
Smoking, n (%)	63 (19.5)	17 (22.4)	0.69
Chronic kidney disease, n (%)	74 (22.9)	25 (32.9)	0.10
Congestive heart failure, n (%)	42 (13.0)	14 (18.4)	0.30
Cerebrovascular disease, n (%)	24 (7.4)	9 (11.8)	0.31
Chronic Obstructive Pulmonary Disease (n (%)	20 (6.2)	9 (11.8)	0.14
Presence of other chronic condition, n (%)	199 (61.6)	57 (75.0)	**0.04**
Number of chronic conditions, mean (SD)	2.02 (1.66)	2.62 (1.62)	0.01
Oxygen saturation* (%), mean (SD)	93.11 (8.19)	88.80 (12.02)	**<0.01**
Emergency Severity Index, mean (SD)	2.13 (0.58)	1.61 (0.59)	**<0.01**
Duration of symptoms (days), mean (SD)	7.55 (11.67)	5.36 (5.19)	0.13
Moderate/Severe effusion, n (%)	6 (1.9)	3 (3.9)	0.50
Moderate/Severe LV systolic function, n (%)	79 (24.5)	22 (28.9)	0.51

Moderate/Severe RV function, n (%)	104 (32.2)	27 (35.5)	0.67
LVEF, mean (SD)	58.00 (13.55)	50.33 (19.74)	**<0.01**
Mitral inflow (E)/ TDI Lateral (E), mean (SD)	9.80 (5.70)	10.18 (6.15)	0.72
TR Velocity, mean (SD)	2.73 (0.50)	2.89 (0.64)	0.15
TV annular motion, mean (SD)	18.82 (4.93)	18.37 (5.71)	0.64

Notes: Percents reflect row percents. P-values obtained from independent samples t-test for continuous variables and chi-square tests for categorical variables. **Abbreviations:** LV: left ventricle; RV: right ventricle; SD: standard deviation; TDI: tissue Doppler imaging. * Pulse oximetry.

Table 2: Model performance, with clinical and clinical plus echocardiographic variables, for different settings.

	Low resource setting: clinical predictors	**Low resource setting: clinical predictors plus ECHO**	**High resource setting: clinical predictors**	**High resource setting: clinical predictors plus ECHO**
n	399	399	262	262
events	76	76	56	56
d.f.	5	8	5	14
AIC	365.29	369.74	262.89	254.44
R^2	0,1	0,08	0,07	0.06 (95% CI 0.03; 0.13)
C-statistic	0,68	0,67	0,66	0.66 (95% CI 0.63; 0.71)
Brier score	0,14	0,15	0,16	0.17 (95% CI 0.16; 0.17)
Calibration intercept	-0,16	-0,31	-0,24	-0.42 (955 CI -0.48; -0.32)
Calibration slope	0,86	0,75	0,79	0.62 (95% CI 0.58; 0.69)
LRT		x^2 = 1.55 | d.f. = 3 | p = 0.671		x2 = 12.38 | d.f. = 9 | p = 0.193

Notes: Results obtained from logistic regression. R2, c-statistic, Brier score and calibration intercept and slope reflect optimism corrected values obtained from bootstrap resampling (500 samples). Smaller sample size available in high resource setting due to one site being unable to obtain quantitative ECHO measures. Values for high resource plus ECHO are the mean (minimum; maximum) values obtained across the 50 multiply imputed datasets. **Abbreviations:** n, sample size;

AIC, Akaike information criterion; CI: confidence interval; LRT, likelihood ratio test; ECHO, echocardiogram; d.f, model degrees of freedom.

Table 3: Odds ratios (OR) and 95% confidence intervals (CI) for in-hospital mortality.

Variables:	Referent	Risk	OR (95% CI)
Clinical predictors			
Age (years)	52	73	2.10 (1.23; 3.62)
Number of comorbid conditions	1	3	1.30 (0.92; 1.85)
Oxygen saturation (%)	90.5	98.0	0.71 (0.58; 0.85)
Gender	Male	Female	1.04 (0.61; 1.78)
Clinical predictors plus echocardiogram			
Age (years)	52	73	2.12 (1.23; 3.64)
Number of comorbid conditions	1	3	1.29 (0.90; 1.84)
Oxygen saturation (%)	90.5	98.0	0.71 (0.59; 0.86)
Gender	Male	Female	1.01 (0.59; 1.75)
Effusion	None/Mild	Moderate/Severe	2.68 (0.53; 13.64)
Left ventricle systolic function	None/Mild	Moderate/Severe	1.01 (0.50; 2.03)
Right ventricle function	None/Mild	Moderate/Severe	1.09 (0.57; 2.10)

Notes: ORs and 95% CIs obtained from logistic regression. ORs for continuous values scaled to reflect the interquartile range odds ratio (i.e., referent = 25th percentile, risk = 75th percentile).

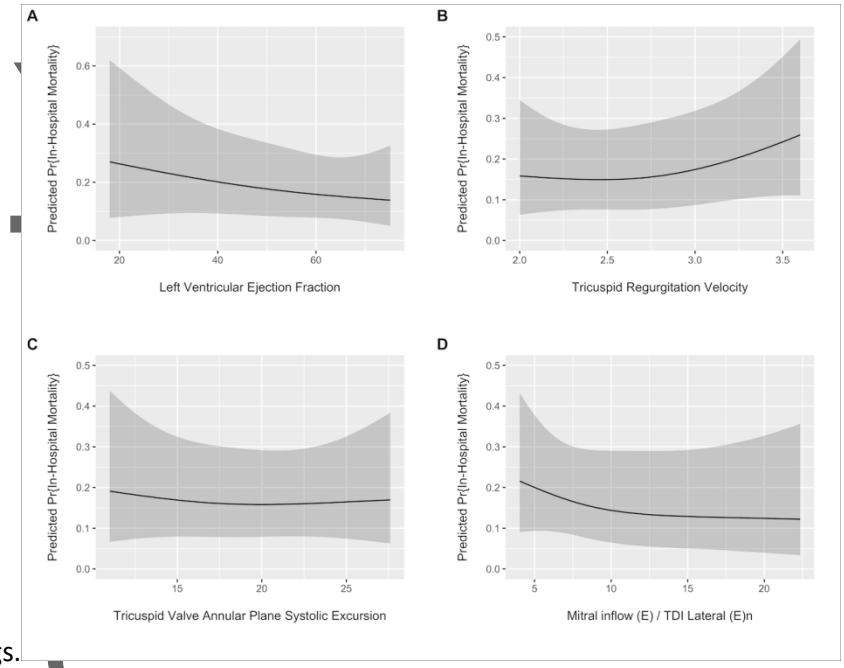
Table 4: Odds ratios (OR) and 95% confidence intervals (CI) for Intensive Care Unit admission.

Variables:	Referent	Risk	OR (95% CI)
Clinical predictors			
Age (years)	52	73	0.67 (0.47; 0.96)
Number of comorbid conditions	1	3	1.22 (0.9; 1.65)
Oxygen saturation (%)	90.5	98.0	0.50 (0.38; 0.66)
Gender	Male	Female	0.75 (0.49; 1.17)
Clinical predictors plus echocardiogram			
Age (years)	52	73	0.65 (0.46; 0.94)
Number of comorbid conditions	1	3	1.28 (0.94; 1.75)
Oxygen saturation (%)	90.5	98.0	0.48 (0.37; 0.64)
Gender	Male	Female	0.74 (0.47; 1.16)
Effusion	None/Mild	Moderate/Severe	1.16 (0.26; 5.11)
Left ventricle systolic function	None/Mild	Moderate/Severe	1.22 (0.66; 2.26)
Right ventricle function	None/Mild	Moderate/Severe	0.41 (0.23; 0.72)

Notes: ORs and 95% CIs obtained from logistic regression. ORs for continuous values scaled to reflect the interquartile range odds ratio (i.e., referent = 25th percentile, risk = 75th percentile).

Figures legends:

Figure 1: Predicted probabilities for in-hospital mortality according to continuous echocardiographic findings.



Supplement figure 1: Calibration curves of predicted versus observed probabilities for in-hospital mortality. A.) Low resource setting with clinical predictors only. B.) Low resource setting with clinical predictors and echocardiography findings. C.) High resource setting with clinical predictors only. D.) High resource setting with clinical predictors and echocardiography findings for single randomly selected imputed dataset.