

## Heart Failure with preserved ejection fraction according to the HFA-PEFF score in COVID-19 patients: clinical correlates and echocardiographic findings

Sara Hadzibegovic\*<sup>1,2,3</sup>, Alessia Lena\*<sup>2,3,4</sup>, Timothy W. Churchill<sup>5,6</sup>, Jennifer E. Ho<sup>7,8</sup>, Sophia Potthoff<sup>2,3,4</sup>, Corinna Denecke<sup>4</sup>, Lukas Rösnick<sup>2,3,4</sup>, Katrin Moira Heim<sup>9</sup>, Malte Kleinschmidt<sup>9</sup>, Leif Erik Sander<sup>9</sup>, Martin Witzzenrath<sup>9</sup>, Norbert Suttorp<sup>9</sup>, Alexander Krannich<sup>10</sup>, Jan Porthun<sup>11</sup>, Tim Friede<sup>12,13</sup>, Javed Butler<sup>14</sup>, Ursula Wilkenshoff<sup>1,15</sup>, Burkert Pieske<sup>3,15,16,17</sup>, Ulf Landmesser<sup>1,3,15</sup>, Stefan D. Anker<sup>2,3,4</sup>, Gregory D. Lewis<sup>8</sup>, Carsten Tschöpe<sup>#2,3,15,16</sup>, Markus S. Anker<sup>#1,2,3</sup>

1 Department of Cardiology Charité - Universitätsmedizin Berlin, Campus Benjamin-Franklin, Berlin, Germany;

2 Berlin Institute of Health Center for Regenerative Therapies (BCRT), Berlin, Germany;

3 German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany;

4 Division of Cardiology and Metabolism, Department of Cardiology, Charité - Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany;

5 Cardiovascular Performance Program, Massachusetts General Hospital, Boston, MA, USA

6 Echocardiography Laboratory, Massachusetts General Hospital, Boston, MA, USA

7 Cardiovascular Research Center, Massachusetts General Hospital, Boston

8 Cardiology Division, Department of Medicine, Massachusetts General Hospital, Boston

9 Department of Infectious Diseases and Respiratory Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany;

10 Clinical Study Center (CSC), Berlin Institute of Health, Charité - Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany;

11 Norwegian University of Science and Technology, Campus Gjøvik

12 Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany

13 German Centre for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany

14 Mississippi State University Jackson Design Center Library, Mississippi, USA;

15 Berlin Institute of Health (BIH) at Charite Berlin, Universitätsmedizin Berlin, Germany;

16 Department of Internal Medicine and Cardiology, Charité - Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany;

17 German Heart Center, Berlin, Germany

\* share the first authorship

# share the last authorship

**Keywords:** COVID-19, diastolic dysfunction, HFA-PEFF, hsTnT, NT-proBNP

**Words:** 3,296 (main text, excl. references and tables)

This article has been accepted for publication and 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/ejhf.2210

**Corresponding author:** Markus S. Anker, Charité - Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany (email: markus.anker@charite.de, Tel.: 004930450553092)

### **Conflict of interest**

**JEH** has received research support from NIH, Gilead Sciences, Bayer AG, and research supplies from EcoNugenics. **TF** reports personal fees from Novartis, Bayer, Janssen, SGS, Roche, Boehringer Ingelheim, Daiichi-Sankyo, Galapagos, Penumbra, Parexel, Vifor, BiosenseWebster, CSL Behring, Fresenius Kabi, Coherex Medical, LivaNova; all outside the submitted work. **JB** is a consultant to Abbott, Adrenomed, Array, Amgen, Applied Therapeutics, Astra Zeneca, Bayer, Boehringer Ingelheim, CVRx, Eli Lilly, G3 Pharma, Impulse Dynamics, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Sequana Medical, V-Wave Limited, and Vifor. **MW** received research support or personal fees outside the current work from German Research Council (DFG), German Ministry of Education and Research (BMBF), European Respiratory Society, Marie Curie Foundation, Else Kröner Fresenius Foundation, Capnetz Foundation, International Max Planck Research School, Actelion, Aptarion, Astra Zeneca, Bayer Health Care, Berlin Chemie, Biotest, Boehringer Ingelheim, Chiesi, Glaxo Smith Kline, Novartis, Noxxon, Pantherna, Quark Pharma, Silence Therapeutics, Sinoxa, Takeda Pharma, Teva, Vaxxilon. **UW** is supported by a Clinical Fellowship Grant from the BIH (Berlin Institute of Health) and has received speaker fees and/or contributions to congresses from Abbott, Astra Zeneca, Bayer, Berlin Chemie, Bristol-Myer Squibb, GE Healthcare, Pfizer, Philips, and Servier. **SDA** reports grants and personal fees from Vifor Int. and Abbott Vascular, and personal fees from Astra-Zeneca, Bayer, Brahms, Boehringer Ingelheim, Cardiac Dimensions, Novartis, Occlutech, Servier, and Vifor Int; all outside the submitted work. **CT** has received speaker fees and/or contributions to congresses from Abbott, Abiomed, Astra Zeneca, Bayer, Berlin Chemie, Novartis, Pfizer, and Servier; all outside the submitted work. All other authors declare no conflict of interest related to the submitted work. **MSA** has received personal fees from Servier, outside the current work.

## ABSTRACT

### Aims

Viral-induced cardiac inflammation can induce heart failure with preserved ejection fraction (HFpEF) like syndromes. COVID-19 can lead to myocardial damage and vascular injury. We hypothesised that COVID-19 patients frequently develop a HFpEF-like syndrome, and designed this study to explore this.

### Methods and Results

Cardiac function was assessed in 64 consecutive, hospitalized, and clinically stable COVID-19 patients from April – November 2020 with left ventricular ejection fraction (LVEF)  $\geq 50\%$  (age  $56 \pm 19$  years, females: 31%, severe COVID-19 disease: 69%). To investigate likelihood of HFpEF presence, we used the HFA-PEFF score. A low (0-1 points), intermediate (2-4 points), and high (5-6 points) HFA-PEFF score was observed in 42%, 33%, and 25% of patients, respectively. In comparison, 64 subjects of similar age, sex, and comorbidity status without COVID-19, showed these scores in 30%, 66%, and 4%, respectively (between groups:  $p=0.0002$ ). High HFA-PEFF scores were more frequent in COVID-19 patients than controls (25% vs. 4%,  $p=0.001$ ). In COVID-19 patients, HFA-PEFF score significantly correlated with age, estimated glomerular filtration rate, high sensitivity troponin T (hsTnT), haemoglobin, QTc interval, LVEF, mitral E/A ratio, and H<sub>2</sub>FPEF score (all  $p<0.05$ ). In multivariate, ordinal regression analyses, higher age and hsTnT were significant predictors of increased HFA-PEFF scores. Patients with myocardial injury (hsTnT  $\geq 14$  ng/L: 31%) vs. patients without myocardial injury, showed higher HFA-PEFF scores (median 5 [IQR 3–6] vs. 1 [0–3],  $p<0.001$ ) and more often showed LV diastolic dysfunction (75% vs. 27%,  $p<0.001$ ).

### Conclusion

Hospitalised COVID-19 patients frequently show high likelihood of presence of HFpEF that is associated with cardiac structural and functional alterations, and myocardial injury. Detailed cardiac assessments including echocardiographic determination of LV diastolic function and biomarkers should become routine in the care of hospitalised COVID-19 patients.

## INTRODUCTION

COVID-19 is known to lead to myocardial damage and vascular injury in many patients. We hypothesised that a substantial proportion of patients with COVID-19 develop heart failure with preserved ejection fraction (HFpEF), and designed this study for further investigation.

The clinical manifestations of COVID-19 disease range from none or mild symptoms to acute respiratory distress syndrome (ARDS) and death<sup>1</sup>. Despite respiratory symptoms, patients also present with chest pain, arrhythmias, palpitations, severe peripheral oedema and acute heart failure<sup>2,3</sup>. In particular, COVID-19 patients with cardiac disease compared to patients without cardiac disease more often have thromboembolic events<sup>4</sup> and demonstrate a higher mortality<sup>5,6</sup>. In May 2020 Tavazzi et al. reported the first case of acute cardiac injury with the finding of SARS-CoV-2 particles and low-grade inflammation within the myocardium but not accompanied by cardiomyocyte necrosis<sup>7</sup>. Whether myocardial alterations are caused by direct viral damage to the heart or vasculature or by infection-related cytokine storm is still under debate<sup>8</sup>. Principally, viral-induced cardiac inflammatory alterations are known to be able to trigger myocarditis induced HFpEF and HFrEF, respectively<sup>9</sup>. There is growing interest in identifying COVID-19 patients at risk of developing viral-related heart failure and cardiovascular (CV) impairments<sup>10</sup>.

## METHODS

### Patients

From April to November 2020, we prospectively enrolled clinically stable COVID-19 patients at one of our COVID-19 wards (at the Department of Internal Medicine/Infectious Diseases and Pulmonary Medicine, Charité-Universitätsmedizin, Campus Virchow-Klinikum, Berlin, Germany) into the observational Cohort Study Pa-COVID-19.<sup>11</sup> All patients gave written informed consent. The study was approved by the ethics committee of the Charité-Universitätsmedizin Berlin (EA2/066/20) and conducted in accordance with the Declaration of Helsinki.

We consecutively recruited 71 clinically stable COVID-19 patients in the first days following their admission to one of our COVID-19 wards at the Charité (average number of days since first symptoms until echocardiography and biomarker assessment 11 days [IQR 5-16]). Six patients were found to have a reduced systolic left ventricular function (left ventricular ejection fraction [LVEF] < 50%, mean LVEF  $35 \pm 6\%$ ) and were therefore excluded from this analysis. Three patients had a transthoracic echocardiogram in the 12 months before their SARS-CoV-2 infection, with one patient showing pre-existing right ventricular dysfunction (TAPSE 12 mm, RV S' 0.06 m/s) with LVEF 50%, who was therefore excluded from the analysis. The final study cohort reported on here consists of 64 COVID-19 patients with an LVEF  $\geq 50\%$  without prior known heart failure.

To compare the HFA-PEFF scores of the COVID-19 patients with that of patients without COVID-19, we included a control group of 64 patients from the Massachusetts General Hospital Cardiopulmonary Exercise Testing (CPET) cohort. Controls were consecutive patients with exertional dyspnoea and preserved ejection fraction (LVEF $\geq 50\%$ ) but without a prior diagnosis of heart failure who were referred for clinically-indicated CPET and also had available echocardiographic and biomarker assessments to calculate HFA-PEFF scores<sup>12</sup>. From this sample of 121 individuals, we group-matched 64 controls for sex (primary matching criterion), age, and comorbidity distribution with the COVID-19 patient cohort. All patients gave written informed consent. The study was approved by the Massachusetts General Hospital's institutional review board (2010P001704) and conducted in accordance with the Declaration of Helsinki.

### **Investigations**

All patients received a standard blood sample from an antecubital vein, and a 12-channel resting electrocardiogram (ECG) and a transthoracic echocardiography (VIVID E95, GE Healthcare) were performed. Data on patients' clinical condition, comorbidities and drug therapy were collected from all patients, directly or from their history and medical records. Myocardial injury was defined as a high sensitivity troponin T (hsTnT) value exceeding the 99<sup>th</sup> percentile of a normal reference population ( $\geq 14$  ng/L)<sup>13,14</sup>.

### **Echocardiographic assessment**

A complete standard echocardiographic examination, including gray-scale images for 2D strain analysis was performed. Offline analyses were conducted with a standard imaging software (EchoPAC SW 203, GE Healthcare). Left ventricular (LV) ejection fraction was calculated using the biplane Simpson's method<sup>15</sup>, left atrial end-systolic volumes were obtained in the apical 4-chamber view according to Simpson's method. Post-processing analysis with speckle-tracking was conducted in the apical 4-chamber, 2-chamber, and long axis views at a frame rate of 50 to 70 frames/s using automated function imaging (AFI). Global longitudinal strain (GLS) was calculated as the mean of all segmental strain values in the 3 apical views.

Linear LV measurements as well as LV mass calculation were performed according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging<sup>16</sup>. LV mass index and left atrium index were obtained by adjustment for body surface area according to DuBois formula.

LV diastolic function was evaluated using: 1) the ratio of early transmitral flow velocity (E) to late transmitral flow velocity (A); 2) the mean (E/e' mean) of transmitral E to early diastolic medial LV tissue velocity (e' septal) and the transmitral E to the early diastolic LV tissue velocity of the lateral wall (e' lateral). Right ventricular function was defined by the measurement of the tricuspid annular plane systolic excursion (TAPSE), and the tricuspid lateral annular systolic velocity (RV S').

Pulmonary artery systolic pressure (PASP) was obtained from the peak velocity of the tricuspid regurgitation jet derived by continuous wave Doppler, using the modified Bernoulli equation, plus the estimated right atrial pressure, obtained from the inferior vena cava size and its collapsibility.

### **HFA-PEFF score**

The HFA-PEFF score was calculated according to the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) recommendations.<sup>17</sup> It is composed of 4 steps (pre-test assessment, echocardiography and natriuretic peptide diagnostic score, functional testing, and final aetiology). According to the HFA-PEFF score the patients were divided into three risk groups for heart failure with preserved ejection fraction (HFpEF) probability: low (0-1 points, HFpEF unlikely), intermediate (2-4, HFpEF uncertain), and high (5-6, HFpEF diagnosis).

## H<sub>2</sub>FPEF score

The H<sub>2</sub>FPEF score was calculated according to Reddy et al.<sup>18</sup>, and derives from the integration of 4 clinical characteristics and 2 echocardiographic parameters. According to this score the diagnosis of HFpEF is ruled out with 0-1 points and highly likely in patients with 6-9 points. The probability of HFpEF is intermediate when the score is between 2-5 points.

## Statistical Analysis

For statistical analyses we used IBM Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Co., Armonk, NY, USA). The collected data were presented as mean  $\pm$  standard deviation or number of patients and percentage. Where mean  $\pm$  standard deviation was not appropriate to summarize the distributions, median and interquartile range (IQR) were reported. We used unpaired t-test/ANOVA as parametric and Mann-Whitney U-Test / Kruskal-Wallis test as nonparametric hypothesis tests. For the analysis of the contingency tables, we preferably used Chi-squared tests. If the contingency tables contained at least one cell assignment smaller than five, the Fisher's Exact test was chosen<sup>19</sup>. We correlated the HFA-PEFF score with clinical relevant parameters from ECG, echocardiography, and blood parameters using rank based Spearman correlation (none of these clinical relevant parameters were used to calculate the HFA-PEFF score). All significant parameters from Spearman correlation analysis were included in a multivariate, ordinal regression analysis with logit link. Prior to multivariate, ordinal regression analysis, six missing "mitral E/A ratios" were imputed using the expectation maximization (EM) algorithm. For the two significant parameters from multivariate regression analysis (hsTnT and age) we conducted receiver operating characteristics (ROC) analysis for predicting a high HFA-PEFF score (5-6 points). The optimal cut-off value was chosen by maximizing Youden's index using the R package maxstat.<sup>20,21</sup> A p-value  $< 0.05$  was considered statistically significant in all analyses. To compare the frequencies of HFA-PEFF scores (in the categories low, middle and high as well as low/middle and high) in COVID-19 patients and controls, chisquare tests were used.

## RESULTS

The final study population included 64 COVID-19 patients. The mean age was  $56 \pm 19$  years and 20 (31%) patients were females. 44 (69%) patients had severe COVID-19 pneumonia according to the current WHO definition<sup>22</sup>. Detailed baseline characteristics are shown in **Table 1**. A total of 3 (5%) patients died during the hospitalization. All other patients were discharged by December 7<sup>th</sup>, 2020 at the latest, with a median hospitalization duration of 10 days (inter quartile range 5-15 days).

In our study we found that 42% of COVID-19 patients (n=27) had a low HFA-PEFF score, 33% (n=21) an intermediate score, and 25% (n=16) a high HFA-PEFF score (**Figure 1**). All COVID-19 patients with a high HFA-PEFF score (n=16 [25%], “5-6 points”) had arterial hypertension and 6 of these patients had atrial fibrillation (**Table 1**). Patients with high HFA-PEFF score (“5-6 points”) had higher levels of hsTnT (+400% vs. “0-1 points on the HFA-PEFF score” and +213% vs. “2-4 points on the HFA-PEFF score”, ANOVA p-value <0.001), lower levels of haemoglobin (-12% vs. “0-1 points” and -6% vs. “2-4 points”, ANOVA p-value =0.032), lower estimated glomerular filtration rate (eGFR) (-31% vs. “0-1” points” and -20% vs. “2-4 points”, ANOVA p-value <0.001), lower LVEF (-5% vs. “0-1 points” and -3% vs. “2-4 points”, ANOVA p-value =0.014), and more often severe COVID-19 disease, diastolic dysfunction or right ventricular dysfunction.

Among the 64 controls with mean age  $59 \pm 16$  years and 39% female, 19 (30%) showed a low HFA-PEFF score, 42 (66%) had an intermediate score, and 3 (4%) had a high HFA-PEFF score (**Figure 1**). The frequency distribution of low/middle/high HFA-PEFF scores was different between COVID-19 patients and controls (chisquare p-value = 0.0002) and high HFA-PEFF scores were more frequent in COVID-19 patients than controls (25% vs. 4%, chisquare p-value = 0.001). Additionally, COVID-19 patients showed higher NT-proBNP values (+101%, p=0.002), and lower LVEF (-3%, p=0.013, **Table 2**).

Spearman correlation analysis showed a positive association between the HFA-PEFF score and the following clinical parameters: age, eGFR, hsTnT, haemoglobin, leukocytes, QTc interval, LVEF, mitral E/A ratio, and additionally with the H<sub>2</sub>FPEF score. None of these parameters were used for the calculation of the HFA-PEFF score (**Table 3**). In multivariate ordinal regression analyses, including the

aforementioned significant clinical parameters, age and hsTnt were significant predictors of the HFA-PEFF score (**Table 4, Figure 2**). If one of these parameters increased by one unit, the HFA-PEFF score increased by 0.06 points (age) or 0.13 points (hsTnt). Nagelkerke's R Square<sup>23</sup> was 0.60, indicative for a substantial goodness-of-fit of the multivariate model according to Cohen.<sup>24</sup> A chi-square was performed to test the difference between the -2 log-likelihood (-2LL) for the intercept-only model and the final model. The statistically significant chi-square statistic ( $p < 0.0001$ ) indicates that the final model gives a significant improvement over the baseline intercept-only model. Correlation coefficient between predicted response category and measured HFA-PEFF score was 0.72 (Spearman's rho). According to Landis and Koch<sup>25</sup>, this is a substantial agreement.

For the two significant parameters from multivariate regression analysis (age and hsTnT), we conducted receiver operating characteristics (ROC) analysis for calculating the best cut-offs for predicting a high HFA-PEFF score (5-6 points; age: area under the curve 0.93 [0.87-1.00]; hsTnT: area under the curve 0.94 [0.89-1.00],  $p < 0.001$ ). The best cut-off for predicting a high HFA-PEFF score regarding age was  $\geq 62$  years (sensitivity 94%, specificity 79%) and for hsTnT  $\geq 10$  ng/L (sensitivity 100%, specificity 79%, **Figure 3**).

Patients with vs. without myocardial injury had higher HFA-PEFF scores (median 5 [IQR 3–6] vs. 1 [IQR 0–3],  $p < 0.001$ ), elevated levels of NT-proBNP (+455%,  $p < 0.001$ ) eGFR (-30%,  $p < 0.001$ , **Table 5**). In echocardiographic examination, patients with myocardial injury demonstrated lower LVEF, more often diastolic dysfunction, and right ventricular dysfunction.

## DISCUSSION

In this study we describe for the first time using the HFA-PEFF score that a substantial proportion of COVID-19 patients showed higher risk of heart failure with preserved ejection fraction (HFpEF). The prevalence of a high HFA-PEFF score was increased in COVID-19 patients in comparison to controls. In multivariate, ordinal regression analyses, age, and hsTnT were significantly associated with a raised HFA-PEFF score. Amongst patients with biochemical evidence for myocardial injury,

HFA-PEFF score was higher and LV diastolic dysfunction and reduced global longitudinal strain were more prevalent. Based on these results using the HFA-PEFF algorithm during the acute phase of infection may facilitate the identification of COVID-19 patients with acute cardiac abnormalities compatible with HFpEF-like syndrome, as is also known for other inflammatory viral diseases.<sup>26</sup>

In the last months, great efforts have been made to accomplish better characterization of the CV profile of COVID-19 patients, to define which factors may reveal CV complications, and how to manage CV care of these patients<sup>27</sup>. So far, CV risk factors like advanced age, male sex, arterial hypertension, and previous coronary artery disease have been frequently reported in COVID-19 patients admitted to hospital<sup>28,29,30</sup>. The presence of arterial hypertension in 43% of our patients is slightly higher than in other large, multi-centre studies conducted in China and United States where hypertension was observed in 24%<sup>1</sup> and 35%<sup>31</sup> of patients with COVID-19.

HFpEF is a severe medical problem with currently limited therapeutic options. The HFA-PEFF score was recently developed to improve the diagnosis of HFpEF<sup>17</sup>. It has been validated in two different independent cohorts of 258 and 459 HFpEF patients<sup>32</sup>, describing a specificity of 93% and positive predictive value of 98% to rule in HFpEF with a high score, and a sensitivity of 99% and a negative predictive value of 73% to rule out HFpEF with a low score. The diagnostic accuracy in patients with  $\geq 5$  points was 0.90 (0.84–0.96, area under the curve of the ROC curve). Accordingly, we reasonably hypothesized the score might be helpful in the assessment of HFpEF like-syndrome in COVID-19 patients.

Echocardiography is an important and non-invasive part of CV examinations in COVID-19 patients<sup>27</sup>. In 1,216 COVID-19 patients assessed with echocardiography, severe cardiac disease was evident in 15%. Myocardial infarction was present in 3%, myocarditis in 3%, and Takotsubo cardiomyopathy in 2%<sup>33</sup>. Szekely et al. observed in a prospective study of 100 COVID-19 patients (29% with severe, 10% with critical, 61% with mild/moderate COVID-19 disease) that LV diastolic dysfunction was present in 16% of patients<sup>34</sup>, whereas we detected diastolic dysfunction in our cohort (69% of patients with severe COVID-19 disease) to be present in 42% of patients with LVEF  $\geq 50\%$ . Hence, LV diastolic dysfunction might be present more often in

patients with severe COVID-19 disease, compared to patients with mild or moderate disease.

In comparison, the H<sub>2</sub>FPEF score was retrospectively derived and validated<sup>35</sup> to discriminate patients with HFpEF from patients with non-cardiac dyspnoea, which is often difficult in clinical practice. Other non cardiac causes of dyspnoea include: chronic obstructive pulmonary disease, COVID-19 and other pneumonia, bronchial asthma, cancer, trauma, angioedema, vocal cord dysfunction, and many others. Up to 25% of all ambulatory patients show dyspnoea<sup>36</sup> and therefore the HFA-PEFF and H<sub>2</sub>FPEF score are important clinical tools in examining patients with unknown causes of dyspnoea. In this study, the HFA-PEFF score and H<sub>2</sub>FPEF score correlated well, even though both scores are very different. While the HFA-PEFF score includes a variety of echocardiographic parameters and laboratory values, the H<sub>2</sub>FPEF score incorporates more clinical characteristics of the patients and fewer echocardiographic parameters. Nonetheless, an intermediate risk for HFpEF according to H<sub>2</sub>FPEF score was found in 36% of the COVID-19 patients while 13% of patients were categorized in the high risk group.

Myocardial injury defined as increased values of hsTnT in COVID-19 patients has been observed in about 20% of COVID-19 patients<sup>37</sup>. It has been shown that higher concentrations of cardiac biomarkers (NT-proBNP, hsTnI, hsTnT) correlate with severity of infection<sup>38,39</sup>. A non-specific increase of cardiac enzymes in COVID-19 patients may reveal not only a predisposition of these patients to cardiac injury<sup>40</sup>, but also other cardiac dysfunctions<sup>41</sup>. In our study hsTnT was observed as a strong predictor of higher HFA-PEFF score. Accordingly, increased hsTnT in COVID-19 patients may help identifying COVID-19 induced cardiac diastolic aberrations.

Whether myocardial injury is only temporary is unclear and therefore clinical follow-up studies of patients with myocardial injury are needed. Cardiac magnetic resonance (CMR) analysing and endomyocardial biopsy studies showed that in some COVID-19 or post-COVID-19 patients an ongoing cardiac inflammation can be detected<sup>42,43,44</sup>. This is in agreement with several echocardiographic parameters, detectable in those patients<sup>45,46</sup>.

The time for cardiac depolarization and repolarization (QTc interval) was prolonged in COVID-19 patients with an intermediate or high HFA-PEFF score. In general, a QTc prolongation is associated with a higher risk for ventricular arrhythmias and sudden cardiac death<sup>47</sup>. Arrhythmias and QTc prolongation are known to occur in COVID-19 patients.<sup>48</sup> Our finding does not necessarily belong directly to key features of LV diastolic dysfunction in COVID-19 induced HFpEF, but could be an indicator of cardiac damage induced by COVID-19 induced cardiac inflammatory stress responses as known for myocarditis and ischemia, respectively<sup>49</sup>. Guo et al.<sup>50</sup> have shown in 187 hospitalized COVID-19 patients that malignant arrhythmias occurred in 7% of patients and were more frequently in patients with vs. without myocardial injury (12% vs. 5%,  $p < 0.001$ ). Hence, the HFA-PEFF score could also be useful and important in detecting COVID-19 patients more vulnerable to malignant arrhythmias.

In this COVID-19 cohort, the in-hospital mortality rate was at 5% (3/64 patients). There are several reasons for this low mortality: first of all, the overall mortality rate during the study period in patients in Germany with a SARS-CoV-2 infection was also low at about 2-5%<sup>51</sup>. Secondly, even though all our patients were hospitalized, we only included clinically stable patients on a normal COVID-19 ward and examined no patients in an intermediate or intensive care unit. Lastly, as explained in the methods section, six patients with LVEF  $< 50\%$  and one patient with previously known right ventricular dysfunction were excluded from the study (two of these seven patients died during hospitalisation). If these patients would have been included in the analysis, the in-hospital mortality rate would have been at 7%. This in-hospital mortality rate is comparable to that found by others in Germany<sup>52</sup>, when looking at hospitalized COVID-19 patients not treated in an intensive care unit (156 deaths in 1,856 patients, i.e. 8%).

Limitations: Our main limitation is the relatively small sample size of 64 COVID-19 patients, but all patients were included prospectively and with detailed echocardiography assessment, which is more complicated to perform in COVID-19 patients than usual, due to the required protection measures for the investigator. Only few patients had ever received an echocardiogram before their current COVID-19 hospitalization ( $n=3$ ) and hence a comparison to previous echocardiograms was not possible. The reason for this is that in none of the included 64 COVID-19 patients,

HFpEF had ever been suspected or diagnosed before. We could only apply step 2 of the HFA-PEFF algorithm in all patients. Since the HFA-PEFF score has not been used in COVID-19 patients before, we did not rule out patients with step 1 (i.e. pre-test assessment), and could not apply step 3 (i.e. stress echocardiography for patients with intermediate scores to secure a final diagnosis of HFpEF) and step 4 (i.e. identify the specific aetiology for HFpEF). The HFA-PEFF score algorithm was assessed during the acute phase of COVID-19 infection. For this setting, the score has not been originally developed. Nevertheless, we believe that our results are representative for the CV profile of clinically stable COVID-19 patients treated in a normal COVID-19 ward despite the small sample size. We cannot know for sure from our analysis, whether HFpEF and COVID-19 are truly related and whether some of the COVID-19 patients already had an elevated HFA-PEFF score before their COVID-19 infection, also given that patients with high HFA-PEFF score were older and all suffered from arterial hypertension, but compared to our control group (with similar age, sex, and comorbidity status), a high HFA-PEFF score was seen more often in COVID-19 patients than controls. It is possible, that patients had undiagnosed HFpEF before their SARS-CoV-2 infection. Although the control group was carefully matched for relevant potential confounders, the presence of some residual confounding can of course not be excluded entirely. To establish whether the HFA-PEFF score could be useful in predicting long-term cardiac dysfunction and whether HFpEF is related or even caused by the SARS-CoV-2 infection, larger studies with long-term follow-up and comprehensive echocardiographic studies of COVID-19 patients are warranted.

We have found evidence of cardiac structural and functional alterations compatible with HFpEF which are associated with presence of myocardial injury in hospitalized COVID-19 patients, detectable by both recently established diagnostic HFpEF-algorithms. Per definition they may belong to the group of viral – induced HFpEF-like syndromes, where aetiology, treatment and probably prognosis differ from classical HFpEF scenarios induced by established risk factors like hypertension or diabetes mellitus, respectively. We suggest that an assessment of cardiovascular status including NTproBNP, hsTnT and LV diastolic function testing by echocardiography is useful to assess the disease status of hospitalized COVID-19 patients.

## TABLE LEGENDS

### Table 1:

\*  $p < 0.05$  vs. HFA-PEFF 2-4 points, \*\*  $p < 0.01$  vs. HFA-PEFF 2-4 points, \*\*\*  $p < 0.001$  vs. HFA-PEFF 2-4 points, #  $p < 0.05$  vs. HFA-PEFF 5-6 points, ###  $p < 0.01$  vs. HFA-PEFF 5-6 points, ###  $p < 0.001$  vs. HFA-PEFF 5-6 points

\$ 16 (89%) of 18 patients already used beta-blockers before hospital admission.

\$\$ 7 (88%) of 8 patients already used diuretics before the hospital admission.

Normal distributed variables are presented as means  $\pm$  SD, non-parametric variables as median (interquartile range) and nominal variables as %.

**Abbreviations:** ACE inhibitors, Angiotensin-converting-enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CRP, C-reactive protein; e', mitral annulus early diastolic velocity; E/A, early filling velocity (E) and late filling velocity (A) ratio through the mitral annulus; LV, left ventricle; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RV, right ventricle; RV S', right ventricle systolic excursion velocity; TAPSE, tricuspid annular plane systolic excursion, Troponin T hs, Troponin T high sensitive; TR, tricuspid regurgitation; WHO, World Health Organization.

### Table 2

Normal distributed variables are presented as means  $\pm$  SD, non-parametric variables as median (interquartile range) and nominal variables as %. The abbreviations are explained in Table 1.

### Table 4:

Link function: Logit. Correlation coefficient between predicted response category and measured HFA-PEFF score: 0.72 (Spearman's rho). \*the Estimate gives the increase or decrease of the HFA-PEFF score, if the given parameter increased by one unit. The abbreviations are explained in Table 1.

### Table 5

Normal distributed variables are presented as means  $\pm$  SD, non-parametric variables as median (interquartile range) and nominal variables as %. The abbreviations are explained in Table 1.

## FIGURE LEGENDS

### **Figure 1: HFA-PEFF score distribution in COVID-19 and controls.**

Comparing the HFA-PEFF scores in the categories low, intermediate and high (low/intermediate and high) between COVID-19 patients and controls results in  $p=0.0002$  ( $p=0.001$ ).

### **Figure 2: Scatter plot of HFA-PEFF score vs Troponin T hs and age**

hsTnT, high sensitive Troponin T

### **Figure 3: Receiver operating characteristics curves for Troponin T hs and age for predicting a high HFA-PEFF Score (5-6 points)**

Area under the curve is 0.94 (0.89-1.00) for Troponin T hs and 0.93 (0.87-1.00) for age.

**Table 1: Baseline characteristics of all COVID-19 patients**

Baseline characteristics	All patients (n=64)	HFA-PEFF 0-1 points (n=27, 42%)	HFA-PEFF 2-4 points (n=21, 33%)	HFA-PEFF 5-6 points (n=16, 25%)	p-value
Age (years)	56 ± 19	46 ± 15 <sup>###</sup>	53 ± 16 <sup>###</sup>	76 ± 11	<b>&lt;0.001</b>
Female sex (n, %)	20 (31)	6 (22)	7 (33)	7 (44)	0.33
BMI (kg/m <sup>2</sup> )	27.1 ± 4.7	26.1 ± 4.4	28.3 ± 5.8	27.3 ± 3.5	0.29
Systolic blood pressure (mmHg)	126 ± 16	124 ± 14 <sup>#</sup>	122 ± 19 <sup>#</sup>	135 ± 14	<b>0.041</b>
Diastolic blood pressure (mmHg)	76 ± 11	75 ± 10	76 ± 12	76 ± 14	0.96
Severe disease according to WHO (n, %)	44 (69)	16 (59) <sup>#</sup>	13 (62) <sup>#</sup>	15 (94)	<b>0.044</b>
Dyspnoea (n, %)	38 (59)	15 (56)	11 (52)	12 (75)	0.33
Peripheral oedema (n, %)	6 (9)	2 (7)	3 (14)	1 (6)	0.64
Total days of hospitalization (n)	10 (5 - 15)	8 (4 - 11)	11 (7 - 19)	13 (8 - 21)	<b>0.021</b>
<b>Medical history</b>					
Arterial hypertension (n, %)	28 (44)	5 (19) <sup>###</sup>	7 (33) <sup>###</sup>	16 (100)	<b>&lt;0.001</b>
Atrial fibrillation (n, %)	8 (13)	0 <sup>##</sup>	2 (10) <sup>#</sup>	6 (38)	<b>&lt;0.001</b>
Coronary artery disease (n, %)	8 (13)	0 <sup>##</sup>	2 (10) <sup>#</sup>	6 (38)	<b>&lt;0.001</b>
Myocardial infarction (n, %)	3 (3)	0 <sup>#</sup>	0 <sup>#</sup>	3 (19)	<b>0.009</b>
Diabetes mellitus type II (n, %)	9 (14)	2 (7)	3 (14)	4 (25)	0.28
Chronic obstructive pulmonary disease (n, %)	7 (11)	1 (4)	3 (14)	3 (19)	0.26
Chronic kidney disease ≥G4 (KDIGO) <sup>53</sup> (n, %)	0	0	0	0	1.00
<b>Cardiovascular medications</b>					
ACE inhibitors (n, %)	7 (11)	0 <sup>##</sup>	1 (5) <sup>#</sup>	6 (38)	<b>&lt;0.001</b>
ARBs (n, %)	8 (13)	1 (4)	3 (14)	4 (25)	0.12
Beta-blockers (n, %) <sup>s</sup>	18 (28)	3 (11) <sup>###</sup>	4 (19) <sup>##</sup>	11 (69)	<b>&lt;0.001</b>
Diuretics (n, %) <sup>ss</sup>	8 (13)	0 <sup>###</sup>	0 <sup>###</sup>	8 (50)	<b>&lt;0.001</b>
<b>Blood parameters</b>					
Sodium (mmol/L)	137 ± 3	138 ± 4	137 ± 3	136 ± 4	0.19

Potassium (mmol/L)	3.8 ± 0.4	3.8 ± 0.3	3.8 ± 0.4	3.8 ± 0.4	0.96
qFR (mL/min)	93.9 ± 24.4	107.1 ± 18.1 <sup>*,###</sup>	92.4 ± 25.3 <sup>##</sup>	73.8 ± 18.4	<b>&lt;0.001</b>
Troponin T hs (ng/L)	8 (5 - 16)	5 (4 - 7) <sup>###</sup>	8 (6 - 12) <sup>##</sup>	25 (15 - 29)	<b>&lt;0.001</b>
NT-proBNP (ng/L)	153 (73 - 509)	74 (21 - 126) <sup>**,###</sup>	162 (92 - 498) <sup>##</sup>	977 (265 - 2817)	<b>&lt;0.001</b>
CRP (mg/L)	27 (8 - 86)	36 (9 - 99)	12 (5 - 60)	25 (10 - 90)	0.36
Haemoglobin (g/dL)	12.5 ± 2.0	13.2 ± 2.1 <sup>##</sup>	12.3 ± 1.8	11.6 ± 1.8	<b>0.032</b>
Leukocytes (/nL)	7.3 ± 3.1	6.6 ± 3.2	8.0 ± 3.1	7.7 ± 2.9	0.30
Thrombocytes (/nL)	280 ± 117	259 ± 113	315 ± 139	268 ± 86	0.24
<b>Resting-ECG parameters</b>					
Sinus rhythm (n,%)	58 (91)	27 (100) <sup>##</sup>	21 (100) <sup>##</sup>	10 (63)	<b>&lt;0.001</b>
Atrial fibrillation (n,%)	4 (6)	0 <sup>##</sup>	0 <sup>#</sup>	4 (25)	<b>0.002</b>
Heart rate (bpm)	76 ± 14	74 ± 12	78 ± 19	74 ± 12	0.74
QRS interval (ms)	100 ± 16	99 ± 9	97 ± 6	107 ± 30	0.14
QTc (ms)	432 ± 28	423 ± 20	437 ± 25	441 ± 38	0.073
QTc ≥ 440 ms (n,%)	23 (36)	5 (19) <sup>*,#</sup>	10 (48)	8 (50)	<b>0.046</b>
<b>Phonocardiographic parameters</b>					
Left Ventricular Ejection Fraction (%)	65 ± 4	66 ± 3 <sup>##</sup>	65 ± 3	63 ± 4	<b>0.014</b>
Global Longitudinal Strain (%)	-16.3 ± 5.7	-16.7 ± 7.8	-17.4 ± 2.1	-14.0 ± 2.8	0.28
HFA-PEFF score (points)	2 (1 - 5)	1 (0 - 1) <sup>**,###</sup>	3 (2 - 4) <sup>#</sup>	5 (5 - 6)	<b>&lt;0.001</b>
H <sub>2</sub> FPEF score (points)	1 (0 - 3)	1 (0 - 1) <sup>###</sup>	1 (1 - 2) <sup>##</sup>	4 (2 - 7)	<b>&lt;0.001</b>
LV wall thickness (mm)	10.6 ± 1.6	9.9 ± 1.2 <sup>###</sup>	10.5 ± 1.6 <sup>###</sup>	11.8 ± 1.5	<b>&lt;0.001</b>
LV mass Index (g/m <sup>2</sup> )	97 ± 28	85 ± 20 <sup>###</sup>	97 ± 23 <sup>#</sup>	115 ± 37	<b>0.003</b>
Relative wall thickness	0.42 ± 0.09	0.39 ± 0.07 <sup>###</sup>	0.42 ± 0.11 <sup>#</sup>	0.47 ± 0.06	<b>0.006</b>
Left atrium volume index (mL/m <sup>2</sup> )	22.9 ± 10.8	18.9 ± 6.1 <sup>###</sup>	22.7 ± 7.2 <sup>#</sup>	29.9 ± 16.6	<b>0.004</b>
Mitral E/A ratio	1.1 ± 0.4	1.3 ± 0.4 <sup>*,##</sup>	1.0 ± 0.5	0.8 ± 0.3	<b>0.008</b>
Diastolic dysfunction (n,%)	27 (42)	3 (11) <sup>***,###</sup>	11 (52)	13 (81)	<b>&lt;0.001</b>
Grade 1 (E/A < 1 + E/e' mean < 10)	19 (30)	3 (11) <sup>***, #</sup>	10 (48)	6 (38)	<b>0.017</b>
Grade 2 (E/A ≥ 1 + E/e' mean 10-14)	4 (6)	0 <sup>#</sup>	1 (5)	3 (19)	<b>0.046</b>

Grade 3 (E/A < 1 + E/e' mean > 14)	4 (6)	0 ##	0 #	4 (25)	<b>0.002</b>
RV dysfunction (TAPSE <18 mm and/or RV S' <0.10 m/s), n (%)	6 (9)	1 (4) ##	0 ##	5 (31)	<b>0.008</b>
Septal e' (cm/s)	8.7 ± 2.8	10.1 ± 2.7 ###	8.8 ± 2.4 ###	6.3 ± 1.7	<b>&lt;0.001</b>
Lateral e' (cm/s)	11.1 ± 3.5	12.9 ± 3.2 ###	11.2 ± 2.2 ###	8.3 ± 2.7	<b>&lt;0.001</b>
TR Velocity (m/s)	2.38 ± 0.42	2.24 ± 0.23 ###	2.29 ± 0.29 ###	2.70 ± 0.59	<b>0.001</b>
Pulmonary artery systolic pressure (mmHg)	28 ± 8	26 ± 4 ###	26 ± 6 ###	33 ± 11	<b>0.010</b>

**Table 2: Analysis of all COVID-19 patients vs controls**

Baseline characteristics	COVID-19 patients (n=64)	Controls (n=64)	p-value
Age (years)	56 ± 19	59 ± 16	0.38
Female sex (n,%)	20 (31)	25 (39)	0.36
NT-proBNP (ng/L)	153 (73 – 509)	76 (36 – 133)	<b>0.002</b>
Sinus rhythm (n,%)	58 (91)	49 (77)	<b>0.032</b>
<b>Medical history</b>			
Arterial hypertension (n,%)	28 (44)	36 (56)	0.16
Atrial fibrillation (n,%)	8 (13)	15 (23)	0.11
Coronary artery disease (n,%)	8 (13)	10 (16)	0.61
Myocardial infarction (n,%)	3 (5)	1 (2)	0.31
Diabetes mellitus type II (n,%)	9 (14)	7 (11)	0.59
Chronic obstructive pulmonary disease (n,%)	7 (11)	5 (8)	0.54
Chronic kidney disease ≥G4 (KDIGO) (n,%)	0	0	1.00
<b>Echocardiographic parameters</b>			
Left Ventricular Ejection Fraction (%)	65 ± 4	67 ± 6	<b>0.013</b>
LV wall thickness (mm)	10.5 ± 1.6	10.2 ± 2.2	0.33
LV mass Index (g/m <sup>2</sup> )	97 ± 28	83 ± 26	<b>0.006</b>
Relative wall thickness	0.42 ± 0.09	0.44 ± 0.11	0.36
Mitral E/A ratio	1.1 ± 0.4	1.2 ± 0.4	0.47
Septal e' (cm/s)	8.7 ± 2.8	7.3 ± 2.0	<b>0.002</b>
Lateral e' (cm/s)	1.1 ± 3.5	1.0 ± 3.0	<b>0.048</b>
TR Velocity (m/s)	2.38 ± 0.42	2.51 ± 0.38	0.087
Pulmonary artery systolic pressure (mmHg)	29 ± 9	35 ± 8	<b>&lt;0.001</b>

**Table 3: Spearman correlation for HFA-PEFF score vs. all other parameters**

	All COVID-19 patients (n=64)	
Measurement	$r_s$ (95% confidence interval)	p-value
Age (years)	0.64 (0.45 – 0.78)	<b>&lt;0.001</b>
BMI (kg/m <sup>2</sup> )	0.16 (-0.09 – 0.40)	0.22
Systolic blood pressure (mmHg)	0.24 (-0.01 – 0.45)	0.056
Diastolic blood pressure (mmHg)	0.13 (-0.09 – 0.35)	0.32
H <sub>2</sub> FPEF score (points)	0.61 (0.41 – 0.77)	<b>&lt;0.001</b>
Sodium (mmol/L)	-0.23 (-0.47 – 0.04)	0.070
Potassium (mmol/L)	0.06 (-0.20 – 0.31)	0.63
eGFR (mL/min)	-0.59 (-0.73 – -0.41)	<b>&lt;0.001</b>
Troponin T hs (ng/L)	0.73 (0.57 – 0.84)	<b>&lt;0.001</b>
NT-proBNP (ng/L)	0.77 (0.65 – 0.85)	<b>&lt;0.001</b>
CRP (mg/L)	-0.10 (-0.36 – 0.14)	0.42
Haemoglobin (g/dL)	-0.34 (-0.57 – -0.08)	<b>0.007</b>
Leukocytes (/nL)	0.27 (0.03 – 0.47)	<b>0.033</b>
Thrombocytes (/nL)	0.15 (-0.09 – 0.39)	0.23
Heart rate (bpm)	-0.01 (-0.23 – 0.22)	0.95
QRS interval (ms)	-0.04 (-0.30 – 0.25)	0.73
QTc (ms)	0.35 (0.08 – 0.56)	<b>0.005</b>
Left Ventricular Ejection Fraction (%)	-0.30 (-0.52 – -0.06)	<b>0.017</b>
Mitral E/A ratio	-0.54 (-0.71 – -0.32)	<b>&lt;0.001</b>

**Table 4: Multivariate ordinal regression analyses**

	Estimate*	Std. Error	p-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Age (years)	0.06	0.02	<b>0.007</b>	0.02	0.11
eGFR (mL/min)	0.01	0.02	0.59	-0.02	0.04
Troponin T hs (ng/L)	0.13	0.04	<b>0.001</b>	0.05	0.20
Haemoglobin (g/dL)	0.05	0.16	0.78	-0.27	0.37
Leukocytes (/nL)	0.09	0.08	0.29	-0.07	0.25
QTc (ms)	0.01	0.01	0.63	-0.02	0.03
LVEF (%)	-0.06	0.08	0.44	-0.22	0.10
Mitral E/A ratio	-0.60	0.74	0.42	-2.05	0.85

**Table 5: Analysis of COVID-19 patients according to myocardial injury (hsTnT >99% ULN/ >14 ng/L)**

Baseline characteristics	Without myocardial injury (n=44, 69%)	Myocardial injury (n=20, 31%)	p-value
Age (years)	50 ± 16	70 ± 17	<b>&lt;0.001</b>
Female sex (n,%)	11 (25)	9 (45)	0.11
BMI (kg/m <sup>2</sup> )	26.8 ± 4.5	27.8 ± 5.3	0.45
Systolic blood pressure (mmHg)	124 ± 17	131 ± 14	0.14
Diastolic blood pressure (mmHg)	76 ± 12	76 ± 11	0.88
Severe disease according to WHO (n,%)	29 (66)	15 (75)	0.47
Dyspnoea (n,%)	25 (57)	13 (65)	0.54
Peripheral oedema (n,%)	4 (9)	2 (10)	0.91
Total days of hospitalization (n)	9 (5 - 14)	13 (9 - 21)	<b>0.016</b>
<b>Medical history</b>			
Arterial hypertension (n,%)	14 (32)	14 (70)	<b>0.004</b>
Atrial fibrillation (n,%)	2 (5)	6 (30)	<b>0.009</b>
Coronary artery disease (n,%)	3 (7)	5 (25)	0.096
Myocardial infarction (n,%)	1 (2)	2 (10)	0.23
Diabetes mellitus type II (n,%)	2 (5)	7 (35)	<b>0.003</b>
Chronic obstructive pulmonary disease (n,%)	3 (7)	4 (20)	0.19
Chronic kidney disease ≥G4 (KDIGO) (n,%)	0	0	1.00
<b>Cardiovascular medications</b>			
ACE inhibitors (n,%)	2 (5)	5 (25)	<b>0.026</b>
ARBs (n,%)	4 (9)	4 (20)	0.24
Beta-blockers (n,%)	7 (16)	11 (55)	<b>0.001</b>
Diuretics (n,%)	0	8 (40)	<b>&lt;0.001</b>
<b>Blood parameters</b>			
Sodium (mmol/L)	138 ± 3	136 ± 3	<b>0.017</b>
Potassium (mmol/L)	3.8 ± 0.4	3.8 ± 0.4	0.86

eGFR (mL/min)	102.9 ± 20.2	74.4 ± 21.6	<b>&lt;0.001</b>
Troponin T hs (ng/L)	6 (5 - 8)	22 (16 - 29)	<b>&lt;0.001</b>
NT-proBNP (ng/L)	97 (33 - 191)	538 (234 - 2414)	<b>&lt;0.001</b>
CRP (mg/L)	24 (7 - 84)	32 (9 - 92)	0.45
Haemoglobin (g/dL)	13.0 ± 1.7	11.4 ± 2.3	<b>0.002</b>
Leukocytes (/nL)	7.0 ± 3.1	8.0 ± 3.2	0.23
Thrombocytes (/nL)	273 ± 127	293 ± 94	0.54
<b>Resting-ECG parameters</b>			
Sinus rhythm (n,%)	44 (100)	14 (70)	<b>0.001</b>
Atrial fibrillation (n,%)	0	4 (20)	<b>0.008</b>
Heart rate (bpm)	75 ± 13	77 ± 17	0.61
QRS interval (ms)	98 ± 9	106 ± 26	0.23
QTc (ms)	428 ± 23	440 ± 34	0.085
QTc ≥ 440 ms (n,%)	13 (30)	10 (50)	0.11
<b>Echocardiographic parameters</b>			
Left Ventricular Ejection Fraction (%)	66 ± 3	63 ± 4	<b>0.013</b>
Global Longitudinal Strain (%)	-16.6 ± 6.4	-15.5 ± 3.0	0.53
HFA-PEFF score (points)	1 (0 - 3)	5 (3 - 6)	<b>&lt;0.001</b>
H <sub>2</sub> FPEF score (points)	1 (0 - 2)	3 (1 - 7)	<b>&lt;0.001</b>
LV wall thickness (mm)	10.2 ± 1.5	11.3 ± 1.6	<b>0.007</b>
LV mass Index (g/m <sup>2</sup> )	92 ± 23	108 ± 35	<b>0.031</b>
Relative wall thickness	0.41 ± 0.09	0.45 ± 0.07	0.061
Left atrium volume index (mL/m <sup>2</sup> )	20.6 ± 6.9	27.9 ± 15.5	0.055
Mitral E/A ratio	1.2 ± 0.5	0.8 ± 0.3	<b>0.004</b>
Diastolic dysfunction (n,%)	12 (27)	15 (75)	<b>&lt;0.001</b>
Grade 1 (E/A < 1 + E/E' mean < 10)	10 (23)	9 (45)	0.071
Grade 2 (E/A ≥ 1 + E/E' mean 10-14)	2 (5)	2 (10)	0.58
Grade 3 (E/A < 1 + E/E' mean > 14)	0	4 (20)	<b>0.008</b>
RV dysfunction (TAPSE < 18 mm and/or RV S' < 0.10 m/s), n (%)	0	6 (30)	<b>0.001</b>
Septal e' (cm/s)	9.4 ± 2.7	7.2 ± 2.5	<b>0.004</b>

# Accepted Article

Lateral e' (cm/s)	12.1 ± 3.2	9.4 ± 3.6	<b>0.004</b>
TR Velocity (m/s)	2.28 ± 0.27	2.59 ± 0.57	<b>0.030</b>
Pulmonary artery systolic pressure (mmHg)	26 ± 5	31 ± 11	<b>0.028</b>

## ACKNOWLEDGMENT

We thank the patients, investigators, nurses, supporting staff, and physicians who were involved in this study. MW is supported by grants from the German Research Foundation, SFB-TR84 C6 and C9, by the German Ministry of Education and Research (BMBF) in the framework of the CAPSyS (01ZX1304B), CAPSyS-COVID (01ZX1604B), SYMPATH (01ZX1906A) and PROVID project (01KI20160A) and by the Berlin Institute of Health (CM-COVID).

## REFERENCES

<sup>1</sup> Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020; 282: 1708-1720.

<sup>2</sup> Bromage DI, Cannata A, Rind IA, Gregorio C, Piper S, Shah AM, McDonagh TA. The impact of COVID-19 on heart failure hospitalization and management: report from a Heart Failure Unit in London during the peak of the pandemic. *Eur J Heart Fail.* 2020;22:978-984.

<sup>3</sup> Fried JA, Ramasubbu K, Bhatt R, Topkara VK, Clerkin KJ, Horn E, Rabbani L, Brodie D, Jain SS, Kirtane AJ, Masoumi A, Takeda K, Kumaraiah D, Burkhoff D, Leon M, Schwartz A, Uriel N, Sayer G. The Variety of Cardiovascular Presentations of COVID-19. *Circulation.* 2020;141:1930–1936.

<sup>4</sup> Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbricatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J.* 2020;41:1821-1829.

<sup>5</sup> Ruan Q, Yang K, Wang W, Jiang L, Song J.. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020;46:846-848.

<sup>6</sup> Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020;5:802-810.

<sup>7</sup> Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, Sepe PA, Resasco T, Camporotondo R, Bruno R, Baldanti F, Paolucci S, Pelenghi S, Iotti GA,

Mojoli F, Arbustini E. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail.* 2020;22:911-915.

<sup>8</sup> Van Linthout S, Klingel K, Tschöpe C. SARS-CoV-2 -related myocarditis-like syndromes Shakespeare's question: what's in a name? *Eur J Heart Fail.* 2020. 22:922-925.

<sup>9</sup> Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, Hare JM, Heidecker B, Heymans S, Hübner N, Kelle S, Klingel K, Maatz H, Parwani AS, Spillmann F, Starling RC, Tsutsui H, Seferovic P, Van Linthout S. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol.* 2020 Oct 12:1-25.

<sup>10</sup> Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: Possible mechanisms. *Life Sci.* 2020.15;253:117723.

<sup>11</sup> Kurth F, Roennefarth M, Thibeault C, Corman VM, Müller-Redetzky H, Mittermaier M, Ruwwe-Glösenkamp C, Heim KM, Krannich A, Zvorc S, Schmidt S, Kretzler L, Dang-Heine C, Rose M, Hummel M, Hocke A, Hübner RH, Opitz B, Mall MA, Röhmel J, Landmesser U, Pieske B, Knauss S, Endres M, Spranger J, Mockenhaupt FP, Tacke F, Treskatsch S, Angermair S, Siegmund B, Spies C, Weber-Carstens S, Eckardt KU, Schürmann D, Uhrig A, Stegemann MS, Zoller T, Drosten C, Suttorp N, Witzernath M, Hippenstiel S, von Kalle C, Sander LE. Studying the pathophysiology of coronavirus disease 2019: a protocol for the Berlin prospective COVID-19 patient cohort (Pa-COVID-19). *Infection.* 2020 Aug;48:619-626.

<sup>12</sup> Churchill TW, Li SX, Curreri L, Zern EK, Lau ES, Liu EE, Farrell R, Shoenike MW, Sbarbaro J, Malhotra R, Naylor M, Tschöpe C, de Boer RA, Lewis GD, Ho JE. Evaluation of 2 Existing Diagnostic Scores for Heart Failure With Preserved Ejection Fraction Against a Comprehensively Phenotyped Cohort. *Circulation.* 2021;143:289-291.

<sup>13</sup> Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497-506.

<sup>14</sup> Gao C, Wang Y, Gu X, Shen X, Zhou D, Zhou S, Huang JA, Cao B, Guo Q; Community-Acquired Pneumonia–China Network. Association Between Cardiac Injury and Mortality in Hospitalized Patients Infected With Avian Influenza A (H7N9) Virus. *Crit Care Med.* 2020;48:451-458.

<sup>15</sup> Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JW. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography*. 2015; 28:1-39.

<sup>16</sup> Lang RM, Badano LP, Mor-Avi V, 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 [published correction appears in *Eur Heart J Cardiovasc Imaging*. 2016;17(4):412] [published correction appears in *Eur Heart J Cardiovasc Imaging*. 2016;17 (9):969]. *Eur Heart J Cardiovasc Imaging*. 2015;16:233-270.

<sup>17</sup> Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail*. 2020; 22: 391-412.

<sup>18</sup> Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018; 138:861–870.

<sup>19</sup> Fisher, R.A. Statistical methods for research workers, in *Breakthroughs in statistics*. Springer, New York, NY, 1921;66-70.

<sup>20</sup> Hothorn, T. (2017). R package maxstat - Maximally Selected Rank Statistics: Hothorn, Torsten. Retrieved from <https://CRAN.R-project.org/package=maxstat>

<sup>21</sup> Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer*, 3, 32-35. doi:[https://doi.org/10.1002/1097-0142\(1950\)3:1](https://doi.org/10.1002/1097-0142(1950)3:1)

---

<sup>22</sup> World Health Organization. (2021). COVID-19 clinical management: living guidance, 25 January 2021. World Health Organization. <https://apps.who.int/iris/bitstream/handle/10665/338882/WHO-2019-nCoV-clinical-2021.1-eng.pdf?sequence=1&isAllowed=y>. (Accessed on 20.04.2021)

<sup>23</sup> Nagelkerke NJD. A note on a general definition of the coefficient of determination. *Biometrika*, 1991. 78, 691–692.

<sup>24</sup> Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, N.J.: Lawrence Erlbaum Associates. 1988.

<sup>25</sup> Landis, J. R., & Koch, G. G. The measurement of observer agreement for categorical data. *Biometrics*, 1977; 33, 159-174.

<sup>26</sup> Tschöpe C, Bock CT, Kasner M, Noutsias M, Westermann D, Schwimmbeck PL, Pauschinger M, Poller WC, Kühl U, Kandolf R, Schultheiss HP. High prevalence of cardiac parvovirus B19 infection in patients with isolated left ventricular diastolic dysfunction. *Circulation*. 2005;111:879-86

<sup>27</sup> <https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance> (Accessed on 15.07.2020)

<sup>28</sup> Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt J-D, Sacco C, Bertuzzi A, Sandri MT, Barco S. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thrombosis Research*. 2020; 191: 9-14.

<sup>29</sup> Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020; 395:1054-1062.

<sup>30</sup> Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of

---

2019 novel coronavirus pneumornia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.

<sup>31</sup> Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, Katz SD, Fishman GI, Kunichoff D, Chen Y, Ogedegbe G, Hochman JS. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19 *N Engl J Med*. 2020;382:2441-2448.

<sup>32</sup> Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca H-P, Henkens M, Heymans S, Beussink-Nelson L, Shah SJ, van Empel VP. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020; 22: 413-421.

<sup>33</sup> Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, White A, Salvo GD, Sade LE, Pearce K, Newby DE, Popescu BA, Donal E, Cosyns B, Edvardsen T, Mills NL, Haugaa K. Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging*. 2020;178:949-958.

<sup>34</sup> Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, Gal Oz A, Rothschild E, Baruch G, Peri Y, Arbel Y, Topilsky Y. The Spectrum of Cardiac Manifestations in Coronavirus Disease 2019 (COVID-19) - a Systematic Echocardiographic Study. *Circulation*. 2020;142:342-353.

<sup>35</sup> Segar MW, Patel KV, Berry JD, Grodin JL, Pandey A. Generalizability and Implications of the H<sub>2</sub>FPEF Score in a Cohort of Patients With Heart Failure With Preserved Ejection Fraction. *Circulation*. 2019;139(15):1851-1853.

<sup>36</sup> Berliner D, Schneider N, Welte T, Bauersachs J. The Differential Diagnosis of Dyspnea. *Dtsch Arztebl Int*. 2016;113:834-845.

<sup>37</sup> Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5:802-810.

---

<sup>38</sup> Han H, Xie L, Liu R, Yang J, Liu F, Wu K, Chen L, Hou W, Feng Y, Zhu C. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. *J Med Virol*. 2020. [Epub ahead of print].

<sup>39</sup> Hu L, Chen S, Fu Y, Gao Z, Long H, Wang JM, Ren HW, Zuo Y, Li H, Wang J, Xu QB, Yu WX, Liu J, Shao C, Hao JJ, Wang CZ, Ma Y, Wang Z, Yanagihara R, Deng Y. Risk Factors Associated with Clinical Outcomes in 323 COVID-19 Hospitalized Patients in Wuhan, China. *Clin Infect Dis*. 2020. [Epub ahead of print].

<sup>40</sup> Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, Cooper LT Jr, Chahal CAA. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*. 2020;17:1463-1471.

<sup>41</sup> Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, Cao S, Liu X, Xiang Y, Zhao Q, Huang H, Yang B, Huang C. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J*. 2020;41:2070-2079.

<sup>42</sup> Puntmann VO, M. Carerj L, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F; Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020. [Epub ahead of print].

<sup>43</sup> Rajpal S, Tong MS, Borchers J, et al. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. *JAMA Cardiol*. 2021;6:116–118.

<sup>44</sup> Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, Bois MC, Lin PT, Maleszewski JJ, Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. *Eur Heart J*. 2020;41:3827-3835.

---

<sup>45</sup> Liu Y, Xie J, Gao P, Tian R, Qian H, Guo F, Yan X, Song Y, Chen W, Fang L, Wu W, Zhang S. Swollen heart in COVID-19 patients who progress to critical illness: a perspective from echo-cardiologists. *ESC Heart Fail.* 2020 Sep 25;7(6):3621–32. doi: 10.1002/ehf2.12873. Epub ahead of print. PMID: 32977359; PMCID: PMC7646648.

<sup>46</sup> Stöbe S, Richter S, Seige M, Stehr S, Laufs U, Hagendorff A. Echocardiographic characteristics of patients with SARS-CoV-2 infection. *Clin Res Cardiol.* 2020;109:1549-1566.

<sup>47</sup> Roden DM. Keep the QT interval: it is a reliable predictor of ventricular arrhythmias. *Heart Rhythm.* 2008;5:1213-5.

<sup>48</sup> Hu TY, Lee JZ, Asirvatham SJ. Cardiovascular Considerations in Coronavirus Disease 2019 with a Special Focus on Arrhythmia. *J Innov Card Rhythm Manag.* 2020;11:4191-4198.

<sup>49</sup> Peretto G, Sala S, Rizzo S, De Luca G, Campochiaro C, Sartorelli S, Benedetti G, Palmisano A, Esposito A, Tresoldi M, Thiene G, Basso C, Della Bella P. Arrhythmias in myocarditis: State of the art. *Heart Rhythm.* 2019;16:793-801.

<sup>50</sup> Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:811-818.

<sup>51</sup> [www.worldometers.info](http://www.worldometers.info)

<sup>52</sup> Ludwig M, Jacob J, Basedow F, Andersohn F, Walker J. Clinical outcomes and characteristics of patients hospitalized for Influenza or COVID-19 in Germany. *Int J Infect Dis.* 2021 Feb;103:316-322.

<sup>53</sup> Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013; 3: 1-150

Figure 1: HFA-PEFF score distribution in COVID-19 patients and controls

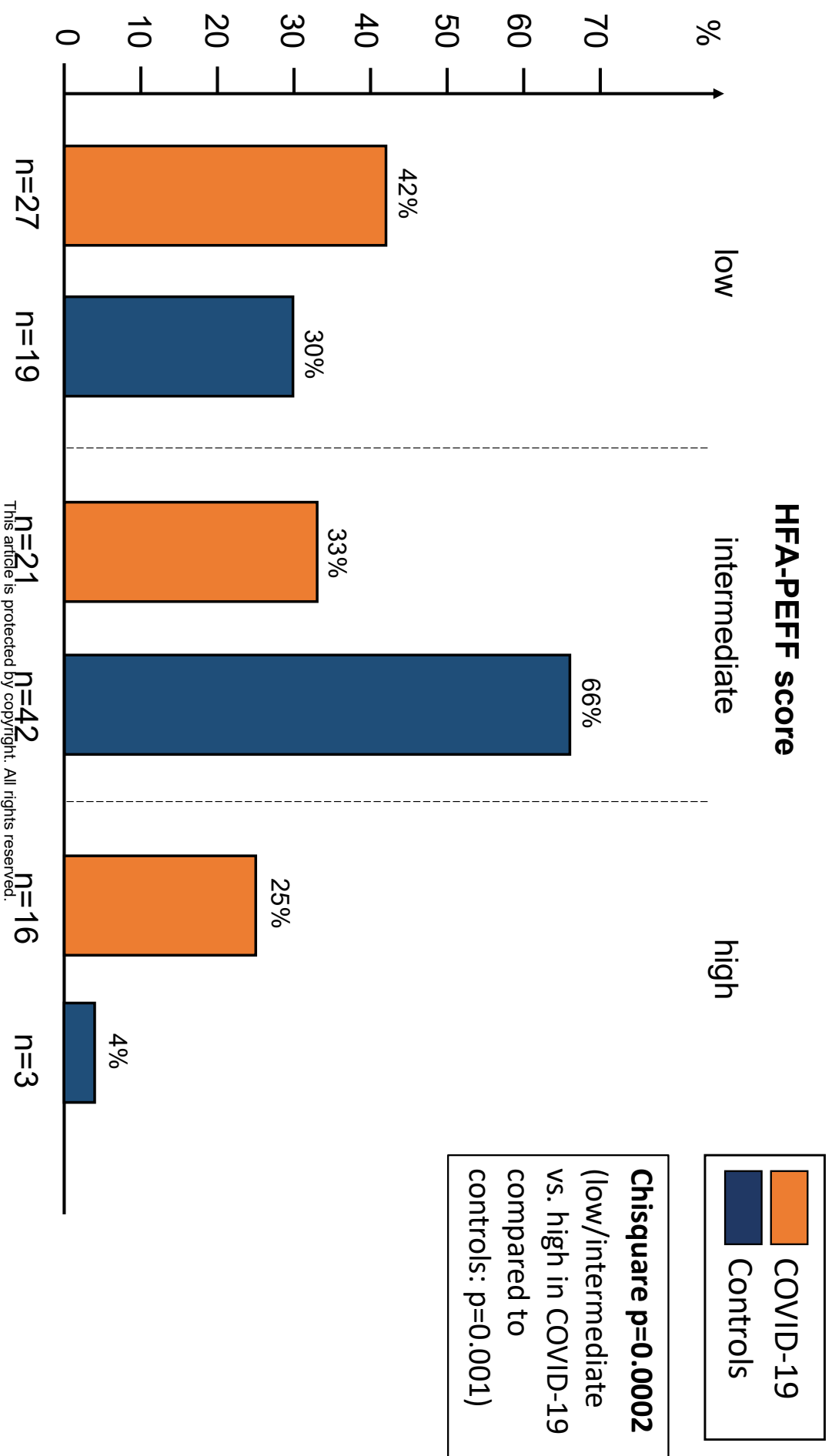
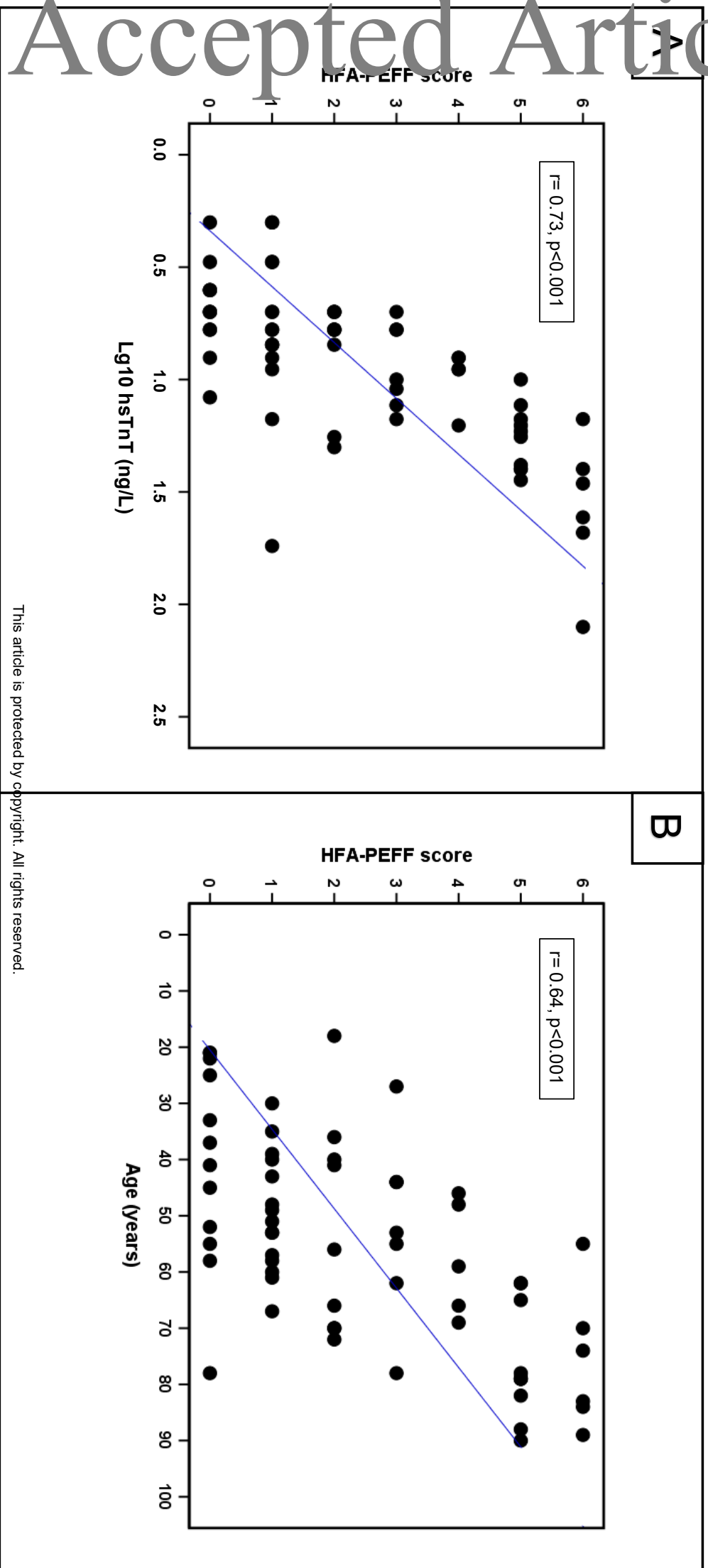


Figure 2: Scatterplots of HFA-PEFF score vs Troponin T hs and age



**Figure 3: Receiver operating characteristics curves for Troponin T hs and age for predicting a high HFA-PEFF Score (5-6 points)**

