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Global Longitudinal Strain to Predict Respiratory Failure and Death in Patients Admitted for COVID-19—Related Disease

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Evidence of the involvement of the cardiovascular system in patients with COVID-19 is increasing. The evaluation of the subclinical cardiac involvement is crucial for risk stratification at admission, and left ventricular global longitudinal strain (LVGLS) may be useful for this purpose. A total of 87 consecutive patients admitted to the COVID Center were enrolled from December 2020 to April 2021. A complete echocardiography examination was performed within 72 hours from admission. The main outcome was the need for mechanical ventilation by way of orotracheal intubation (OTI) and mortality, and the secondary outcome was the worsening of the respiratory function during hospitalization, interpreted as a decrease of the ratio between the partial pressure of oxygen and the fraction of inspired oxygen (P/F) < 100. Of 87 patients, 14 had severe disease leading to OTI or death, whereas 24 had a P/F < 100. LVGLS was significantly impaired in patients with severe disease. After adjustment for risk factors, by considering LVGLS as continuous variable, the latter remained significantly associated with severe acute respiratory distress syndrome (P/F < 100) (hazard ratio [HR] 1.48, 95% confidence interval [CI] 1.18 to 1.88, \(p = 0.001\)) and OTI/death (HR 1.63, 95% CI 1.13 to 2.38, \(p = 0.012\)). When using an LVGLS cutoff of \(-16.1\)%, LVGLS \(\geq -16.1\)% was independently associated with a higher risk of severe acute respiratory distress syndrome (HR 4.0, 95% CI 1.4 to 11.1, \(p = 0.008\)) and OTI/death (HR 7.3, 95% CI 1.6 to 34.1, \(p = 0.024\)). LVGLS can detect high-risk patients at the admission, which can help to guide in starting early treatment of the admitted patients. © 2021 Elsevier Inc. All rights reserved. (Am J Cardiol 2022;165:109–115)

COVID-19 is a pandemic viral infection leading to SARS-CoV-2. Although this respiratory syndrome is the most important cause of death, increasing evidence indicates that the cardiovascular system is affected by this disease. Recently, the echographic measurement of left ventricle (LV) deformation by global longitudinal strain (GLS) has been introduced as a novel marker of cardiac dysfunction. It evaluates myocardial deformation and is less influenced by loading conditions compared with ejection fraction (EF). Accumulating literature on multimodal cardiac imaging highlights the LV GLS (LVGLS) impact on the prognosis of several clinical conditions. Moreover, LVGLS can detect initial and subclinical ventricle impairment, earlier than conventional echocardiographic parameters. The evaluation of the subclinical cardiac involvement in patients with COVID-19 may be crucial and LVGLS may be useful for this purpose. Our study investigates whether LVGLS was a predictor of the decrease of respiratory function, the need for mechanical ventilation, and mortality in patients admitted to the hospital with COVID-19—related infection.

Methods

A single-center, prospective study was performed at the University Hospital of Verona, Italy. We enrolled a total of 87 consecutive patients admitted to the COVID Center Unit (Internal Medicine and Infectious Disease wards) from December 2020 to April 2021. All admitted patients received bedside echocardiography within 72 hours from admission to the COVID Center Unit. The study was approved by the local Ethics Committee. Inclusion criteria were: age \(\geq 18\) years; hospitalization with a confirmed diagnosis of COVID-19; EF \(\geq 50\)%. Exclusion criteria were: history of ischemic cardiomyopathy; the presence of LV segmental wall-motion abnormalities; history of heart failure; severe valvular disease; atrial fibrillation; pulmonary hypertension, chronic obstructive pulmonary disease. Upon admission, complete bloodwork, including the markers presented in this study, was performed. A database including demographic characteristics, comorbidities, laboratory exams, and outcomes was independently reviewed by a medical team using the electronic database. The respiratory impairment was assessed using the ratio between the partial
pressure of oxygen and the fraction of inspired oxygen (P/F) obtained by arterial blood gas analysis.

Parasternal axis, apical views, and subxiphoid view were obtained using a GE Vivid T8 ultrasound system (GE Healthcare, Arlington Heights, Illinois), (GLS normal values −18.2% to −21.2%). A digital loop, electrocardiographic gated, was acquired from 2 to 3, and 4 chamber views. All images were stored and analyzed at a later time. LVGLS was calculated by averaging the values obtained in the apical 2 to 3 and 4 chamber views (18 segments). LV endocardial borders were automatically traced at the end of the diastole, subsequently, the software tracked the endocardial layer throughout the cardiac cycle. When necessary, the operator manually adjusted the endocardial border. A segment could be excluded by the operator if it was judged not well traced (Figure 1). All measurements were made blinded to other laboratory and clinical data, including patient outcomes.

Two different outcomes were considered in our study: the main outcome was the need of orotracheal intubation (OTI) and mortality, whatever came first; the secondary outcome was the development of severe acute respiratory distress syndrome (ARDS) (P/F <100 mm Hg) during hospitalization.

Continuous variables are presented as mean ± SD or median with interquartile range based on data distribution. Categorical variables are expressed as percentages. One-way analysis of Variance or Kruskal–Wallis were used to compare continuous variables according to the data distribution pattern. Logistic and Cox regression analyses were performed to determine if any anamnestic, clinical, or imaging variable (age, gender, hypertension, diabetes, chronic kidney disease, d-dimer, ferritin, ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/E’), and LVGLS) could be independently associated with the dependent variable (end points). The variable selection was made through sequential replacement (a stepwise method), which consists of a combination of backward and forward techniques. If the p value was <0.05 or >0.1, the covariates were respectively included and excluded from the regression model. The area under the receiver operating characteristic (ROC) curves were built to assess the performance of LVGLS (alone and together with the other dependent variables included in the model) for predicting the study end points. Furthermore, we tried to identify the optimal cut-off point of LVGLS for the prediction of the outcomes, trying to optimize sensibility and specificity in the C-statistics analysis. IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp. Released 2013, Armonk, New York) was used for all data analysis. All tests were 2-sided, and p <0.05 were considered statistically significant.

Results

A total of 87 consecutive patients were enrolled in our study. Baseline anthropometric, clinical, biochemical parameters, and echocardiography data are listed in Tables 1 and 2. Regarding specific medical therapy for COVID-19, 90% of subjects were treated with steroids, 18.8% with remdesivir, 24.4% received antibiotics, and all patients were treated with low molecular weight heparin. Patients with lower LVGLS had higher N-terminal pro brain natriuretic peptide (r = 0.58, p <0.001), no correlations were found between LVGLS and other biochemical and imaging parameters. When patients were divided into 2 subgroups

![Figure 1. LVGLS with the bull’s eye obtained from 2 to 3 and 4 CH in patients with COVID-19. LVGLS was calculated by averaging the values of the 3 views. ANT = anterior; CH = chamber; GS = global strain; INF = inferior; LAT = lateral; POST = posterior; SEPT = septum.](image)
according to the end points of the study: OTI or death (n = 14; Table 1); development of severe ARDS (P/F < 100 mm Hg) (n = 24; Table 2), LVGLS was statistically significant impaired in both outcomes. ROC curves were elaborated for both end points to obtain the area under the curve, either considering LVGLS alone or on top of the other covariates after the regression models. In patients with the P/F lower than 100, LVGLS alone predicted the outcome with 78% accuracy (95% CI 0.66 to 0.88). The addition of LVGLS into the model with clinical and imaging predictors resulted in a significant increase in the C-statistic (from 0.64 to 0.85, p < 0.05) (Figure 2). When considering the OTI/death end point, LVGLS alone predicted the outcome with 74% accuracy (95% CI 0.68 to 0.87). The addition of LVGLS into the model with clinical and imaging predictors resulted in a nonsignificant increase in the C-statistic (from 0.73 to 0.93; p > 0.05) (Figure 2). In the Cox regression analyses, considering LVGLS as a continuous variable, this remained independently predictive of severe ARDS (P/F <100) (HR 1.48, 95% CI 1.18 to 1.88, p = 0.001) and OTI/death (HR 1.63, 95% CI 1.13 to 2.38, p = 0.012). When using an LVGLS cutoff of −16.1% (sensitivity 86.5%, specificity 58.5% by the ROC curve), LVGLS ≥ −16.1% was independently associated with a higher risk of severe ARDS (HR 4.0, 95% CI 1.4 to 11.1, p = 0.008) and OTI/death (HR 7.3, 95% CI 1.6 to 34.1, p = 0.024) (Figure 3). Ferritin was a significant predictor of both outcomes (HR 1.001, 95% CI 1.000 to 1.002, p = 0.029), whereas the E/E' ratio was significant only in the OTI/death outcome (HR 1.62, 95% CI 1.12 to 2.36, p = 0.014).

**Discussion**

In this study, we report a strong correlation between the impairment of the LV longitudinal function, measured by LVGLS, with a worse prognosis in patients hospitalized for SARS-CoV-2 infection. Indeed, LVGLS measured at the moment of admission was a strong predictor of respiratory failure and mortality. Notably, in our study we excluded all patients with a history of heart or chronic pulmonary, to
exclude all possible confounding factors that may be associated with poor outcomes.

Cardiac injury is often seen in patients with COVID-19 disease and it is correlated to increased mortality, although only a small percent of patients with COVID-19 experience myocardial involvement. So far, only a few studies have investigated GLS in patients with COVID-19. Xie et al showed that 4 chamber longitudinal strain is associated with cardiac injury and predicts higher mortality. It also seems that biventricular longitudinal strain may improve 3 months after discharge. The ECHOVID-19 study demonstrated that LVGLS is reduced in patients infected with SARS-CoV-2 compared with matched controls and correlates with COVID-19-related death. A recent meta-analysis, including left and right longitudinal strain, showed that patients with poor outcomes had lower GS, and each 1% decrease in LVGLS was associated with a 1.3 \times increased risk of mortality. This result is consistent with what we observed in our study. Croft et al found that LVGLS was reduced in patients with COVID-19 but it was not significantly lower in those who died compared with survivors. However, the Cox regression analysis showed a trend in the ability of LVGLS to predict the need for mechanical ventilation or death. The limited sample size of the study, given that images for measurement of LVGLS were collected only in 56% of the patients, did not probably allow to reach the statistical significance.

Although troponin is a good biomarker of myocardial injury, in our study troponin was not a predictor of mortality. Thus, it remains to be determined whether SARS-CoV-2 affects the myocardium directly or the cardiac impairment is related to the systemic consequences of COVID-19. It has been demonstrated that systemic inflammation increases the metabolic demand, leading to cardiac stress. Our findings suggest that cardiac damage is preferentially associated with LV longitudinal fibers dysfunction because of the inflammatory process, rather than ischemic stress. Probably because of their subendocardial location, the myocardial fibers are highly sensitive to disturbance by various noxae. Longitudinal function plays a fundamental role in cardiac systole by reducing the longitudinal LV size as the mitral annulus is pulled toward the apex. For these reasons, GLS is a sensitive marker of LV dysfunction, regardless of LV function. We hypothesize that SARS-CoV-2-induced systemic inflammation may induce longitudinal cardiac dysfunction from the early stages of the disease.

### Table 2
Baseline characteristics of patients grouped according to the secondary outcome

| Variable                              | PaO2/FiO2 ratio | p value |
|---------------------------------------|-----------------|---------|
|                                       | < 100 (n=24)    | > 100 (n=63) |
| Age (years)                           | 71.5 [60.5; 81.7] | 63.0 [53.0; 73.0] | 0.033 |
| Male sex                              | 73%             | 67%     | 0.023 |
| Body mass index (kg/m²)               | 26.3 [24.3; 28.1] | 26.5 [24.5; 29.2] | 0.849 |
| Hypertension                          | 63%             | 33%     | 0.013 |
| Dyslipidemia                          | 21%             | 21%     | 0.987 |
| Chronic kidney disease                | 17%             | 11%     | 0.492 |
| Diabetes mellitus                     | 8.0%            | 16%     | 0.386 |
| ACE inhibitors-angiotensin receptor blocker | 54%           | 29%     | 0.026 |
| Beta-blockers                         | 38%             | 19%     | 0.054 |
| Systolic blood pressure (mm Hg)       | 120.0 [111.2; 130.0] | 130.0 [115.0; 140.0] | 0.247 |
| Diastolic blood pressure (mm Hg)      | 70.0 [60.0; 80.0] | 75.0 [70.0; 80.0] | 0.309 |
| Heart rate (bpm)                      | 82 [71; 90]     | 75 [70; 88] | 0.313 |
| C-reactive protein (mg/dL)            | 86.5 [33.0; 164.5] | 69 [26; 135] | 0.172 |
| Procalcitonin (ng/mL)                 | 0.18 [0.07; 0.35] | 0.08 [0.05; 0.27] | 0.077 |
| D-dimer (µg/L)                        | 1150 [868; 1903] | 1128 [623; 2300] | 0.548 |
| Ferritin (µg/L)                       | 809 [552; 2056] | 850 [413; 1322] | 0.430 |
| Lymphocytes (mm³)                     | 820 [580; 1205] | 800 [590; 1200] | 0.922 |
| Creatine-kinase (U/L)                 | 1.08 [1.01; 1.15] | 1.09 [1.01; 1.19] | 0.776 |
| Lactic dehydrogenase (U/L)            | 93 [57; 163]    | 67 [39; 157] | 0.149 |
| Troponin (ng/L)                       | 348 [272; 446] | 308 [271; 379] | 0.045 |
| N-terminal pro brain natriuretic peptide (pg/mL) | 16 [9; 26] | 12 [7; 16] | 0.104 |
| Glomerular filtration rate (ml/min)   | 66 [54; 77]     | 80 [66; 100] | 0.011 |
| Alanine aminotransferase (U/L)        | 38 [19; 50]     | 28 [19; 50] | 0.785 |
| Heart rate (bpm)                      | 105 [83; 126]   | 97 [73; 114] | 0.200 |
| Left ventricular end diastolic volume (ml) | 88 [73; 108] | 73 [58; 86] | 0.025 |
| Ejection fraction (%)                 | 60.5 [55.2; 66.5] | 62.1 [57.0; 68.2] | 0.447 |
| Left atrial volume indexed (ml/m²)    | 22.3 [14.9; 25.6] | 21.0 [15.6; 28.6] | 0.958 |
| Right atrial volume (ml)              | 26.0 [23.2; 37.1] | 32.0 [19.7; 45.5] | 0.373 |
| E/A                                   | 0.88 [0.73; 1.05] | 1.00 [0.78; 1.23] | 0.244 |
| E/E'                                  | 7.54 [5.2; 10.4] | 6.7 [5.3; 8.1] | 0.038 |
| Right ventricular diameter (mm)       | 34.1 [31.2; 39.0] | 34.0 [31.0; 38.0] | 0.753 |
| TAPSE (mm)                            | 22.5 [19.2; 33.7] | 26.0 [21.0; 29.0] | 0.116 |
| Systolic pulmonary artery pressure (mm Hg) | 24.2 [15.7; 33.7] | 23.0 [16.6; 28.5] | 0.599 |
| Left ventricular global longitudinal strain (%) | -14.1 [-13.4; -16.1] | -16.8 [-15.1; -18.6] | <0.001 |
Indeed, ferritin, a marker of systemic inflammation was a predictor of both outcomes in the Cox regression. This is consistent with the hypothesis that the mechanism of cardiac injury during COVID-19 disease can be because of the systemic inflammatory response and the immune dysregulation triggered by SARS-CoV-2. This is not surprising because strain imaging can detect subclinical myocardial dysfunction in the preclinical model of sepsis. For instance, Li et al. showed that in rabbits GLS decreased after 2 hours after endotoxin injection, whereas Hestenes et al. demonstrated a reduction of GLS after *Escherichia coli* infusion in pigs. In a clinical setting, a meta-analysis including 794 patients with sepsis, showed that LVGLS was associated with survival, whereas LV EF was not a predictor of mortality. For these reasons, we believe that LVGLS can be affected not only by direct cardiac damage, which is monitored by troponin levels but also by the systemic consequences of infection. In agreement with this hypothesis, some studies showed that LVGLS is affected independently from troponin level. For instance, elevated troponin was not associated with LVGLS in patients with COVID-19, moreover, Lairez et al. showed that there was no differ-

Figure 2. ROC curve showing accuracy of LVGLS and other clinical and imaging risk factors in the 2 end points. Addition of LVGLS into the model with clinical and imaging predictors resulted in a significant increase in the C-statistic in the P/F <100 end point. LVGLS (dotted line), clinical and imaging predictors (other covariates: dashed line), LVGLS plus covariates (solid line). AUC = area under the curve.

Figure 3. Cox regression analysis showing the cumulative incidence of LVGLS events stratified by −16.1% in the 2 end points. LVGLS < −16.1% (solid line), LVGLS ≥ −16.1% (dotted line).
ence in LVGLS in patients without COVID-19, with COVID-19 and with COVID-19 plus increased cardiac troponin. Although it remains unclear if SARS-CoV-2 attacks the heart directly, it does not change the fact that LVGLS remains a strong predictor of hard outcomes in patients with COVID-19.

In the present work, we also evaluated the power of LVGLS to predict the decrease of P/F to <100 mm Hg during the hospitalization, a sign of severe ARDS. In this case, LVGLS improved the prognostic power; this is clearly illustrated by ROC curves showing, with a clear trend, that LVGLS provides prognostic information incremental to common clinical risk factors. To the best of our knowledge, no other reports have studied the capability of LVGLS to predict severe respiratory failure. We hypothesize that such prediction power is related to the LVGLS capability to monitor the right ventricle dysfunction. In patients with COVID-19, multiple elements concur to right ventricle dysfunction: inflammation that causes right ventricle overload and damage,27 ARDS, negative inotropic effects of cytokines, and direct angiotensin-converting Enzyme 2-mediated cardiac injury upon activation by SARS-CoV-2.28 As a consequence of right ventricle dysfunction, the LV function is affected by ventricular interdependence and paradoxical septum. Limited information is available regarding the role of GLS in ARDS. For instance, Lemarié et al29 evaluated the longitudinal function of the right ventricle in patients with ARDS, but they did not find any difference in terms of survival, however, the number of the included patients was low with a low mortality rate. Moreover, they only did a single measurement at 1 time point and it is hard to think that this can predict the long-term outcome, especially in the complex setting of critical care. We believe that left and right GLS can be useful and powerful markers in patients affected by ARDS, even for the prediction of respiratory failure as demonstrated in this report. Further studies are, however, needed to assess the exact role of GLS in patients with ARDS.

In conclusion, our findings show that LVGLS can represent a novel and early marker of cardiac dysfunction, even in low-risk patients without cardiac diseases, which can predict mortality and respiratory failure in patients with COVID-19. For this reason, because of the fast and noninvasive methodology, and the low cost of echocardiography and LVGLS, we propose its assessment in patients admitted for COVID-19-related disease and in patients with ARDS. LVGLS is crucial to unmask subclinical cardiac dysfunction, especially in patients with preserved EF, allowing to identify, at the moment of the admission, high-risk patients who are not otherwise identified. Moreover, there are not many therapeutic options for patients with COVID-19 (i.e., monoclonal antibody, new coming antiviral medications) and LVGLS can be crucial for risk stratification and therefore for decision-making on early treatment at the moment of admission.

This study, however, presents some limitations. First, this is a single-center study and therefore the sample size, although consistent with other similar studies, is limited; second, systemic inflammation was only partially studied; third, right ventricle GLS and atrial strain were not evaluated. Larger studies are needed to confirm and expand the present results.

Disclosures
The authors have no conflicts of interest to declare.

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