

Sustained right ventricular dysfunction in severe COVID-19: The role of disseminated intravascular coagulation

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Abstract

Background: Acute right ventricular (RV) failure is common in patients hospitalized with COVID-19. Compared to the conventional echocardiographic parameters, right ventricular longitudinal strain (RVLS) is more sensitive and accurate for the diagnosis of RV systolic dysfunction.

Objective: Our purpose was to investigate the sustained RV dysfunction echo-quantified by RVLS in patients recovered from severe COVID-19. Furthermore, we aimed to assess whether disseminated intravascular coagulation (DIC) has a key role to predict the impaired RV strain.

Methods: Of 198 consecutive COVID-19 patients hospitalized from March 1, 2020, to April 15, 2020, 45 selected patients who survived from severe COVID-19 were enrolled in the study and referred to our echo-lab for transthoracic echocardiography 6-months after discharge. RVLS was calculated as the mean of the strain values of RV free wall. DIC was defined with a validated scoring system: DIC score equal to or more than 5 is compatible with overt-DIC. Categories of acute respiratory distress syndrome (ARDS) were defined based on PaO₂/FiO₂ ratio.

Results: A total 26 of 45 patients showed impaired RVLS at 6-months' follow-up. DIC score was significantly higher in patients with worse RVLS than in those with better RVLS ($4.8 \pm .5$ vs. $3.6 \pm .6$, $p = .03$). Stages of ARDS did not modulate this relationship. Finally, overt-DIC results the only independent predictor of sustained RV dysfunction (OR 1.233, 95% CI 1.041–1.934, $p = .043$).

Conclusions: Sustained RV impairment frequently occurs in patients recovered from severe COVID-19. DIC plays a key role, resulting in an independent predictor of sustained RV dysfunction.

KEYWORDS

COVID-19, disseminated intravascular coagulation, right ventricular longitudinal strain, SARS-CoV-2, speckle tracking echocardiography

Abbreviations: 2D, two-dimensional; ARDS, acute respiratory distress syndrome; CAC, COVID-19-associated coagulopathy; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; FAC, fractional area change; PASP, pulmonary artery systolic pressure; RV, right ventricular; RVLS, right ventricular longitudinal strain; S', tricuspid lateral annular systolic velocity; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STE, speckle-tracking echocardiography; TAPSE, tricuspid annular plane systolic excursion

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a current pandemic infection caused by a positive-sense RNA virus named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). More than 130 million people have been diagnosed with COVID-19 worldwide.¹ The clinical spectrum of COVID-19 appears to be wide, encompassing asymptomatic infection, mild upper respiratory tract illness, and acute respiratory distress syndrome (ARDS), the most severe form of acute lung injury.^{2,3} Recent reports suggest that acute right ventricular (RV) dysfunction is also common in patients hospitalized with COVID-19 as a direct consequence of elevations in RV afterload due to pulmonary embolism or pneumonia.⁴ Moreover, in-hospital adverse RV remodeling (dysfunction/dilation) has been demonstrated to be of prognostic value.⁵ These observations are aligned with those of a large prospective international registry of 1216 inpatients with COVID-19.⁶ Data are also available about sustained RV involvement in patients after their recovered from COVID-19.^{7,8} However, most of them had moderate type or did not even require hospitalization, making these findings unreliable to reflect the full spectrum-covering patients with critical COVID-19. Furthermore, there are no data about sustained impairment of RV function in patients recovering from severe COVID-19. Two-dimensional speckle-tracking echocardiography (2D-STE) is a non-Doppler method for the objective quantification of LV myocardial deformation from two-dimensional standard echocardiographic images. Because of its capability to detect subclinical impairment of cardiac function, 2D-STE has further been extensively applied to investigate RV function in different clinical settings. Compared to the conventional echocardiographic parameters, RV longitudinal strain (RVLS) derived from 2D-STE is more sensitive and accurate for the diagnosis of RV systolic dysfunction.⁹ It has also been proven to be of clinical value in patients hospitalized with COVID-19.¹⁰ Accumulated evidence reveals that an acquired syndrome known as COVID-19-associated coagulopathy (CAC) is common as part of the systemic inflammatory response syndrome, and disseminated intravascular coagulation (DIC)-like massive intravascular clot formation is frequently seen in the most severely ill patients.^{11,12} Despite its established prognostic value in the acute setting, whether DIC has a relationship with sustained RV dysfunction in severely ill patients who survive their illness remains unknown. Furthermore, whether categories of ARDS could modulate this relationship has not been explored yet. Accordingly, the purpose of the present study was to establish the evidence of sustained RV dysfunction echo-quantified by RVLS in patients recovered from severe type, refining the role of DIC as a potential predictor of impaired RV strain.

2 | METHODS

2.1 | Study design and population

This was a single-center, observational study performed at Baggiovara hospital (Modena, Italy). All consecutive patients with laboratory-

confirmed COVID-19 infection admitted into the hospital from March 1, 2020, to April 15, 2020, were screened for eligibility for this study. A positive laboratory test for SARS-CoV-2 infection was defined as a result of the real-time reverse transcription-polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs.¹³ The examination was implemented in a local laboratory with the adjunct of RT-PCR assays. Patients who met the following criteria were retrospectively included and referred to our division for transthoracic echocardiography 6-months after discharge: 1) age ≥ 18 years; 2) development of ARDS in COVID-19 related pneumonia; 3) recovery according to guidelines from WHO on clinical management, that is, normal temperature lasting longer than 3 days, resolved respiratory symptoms, and two consecutive negative RT-PCR test results separated by at least 24 h. Exclusion criteria were history of cardiomyopathy, myocardial infarction, severe valvular heart disease, malignancy, chronic obstructive pulmonary disease, and chronic kidney disease treated with hemodialysis. Furthermore, patients in whom poor echocardiographic windows were noted at the time of echocardiographic examination were also excluded. Clinical investigations were conducted according to the principles of the Declaration of Helsinki. The study was approved by the Institutional Ethical Board of the "Emilia Nord Area" (Approval number 530/2020/OSS/AOUMO SIRER ID 334). All subjects gave written informed consent for additional research tests and the use of their data for research purposes.

2.2 | Data collection

Clinical data were carefully obtained by reviewing each patient's medical records. Demographics included cardiovascular indices and baseline medication regimen at the time of hospital admission, as was subsequent inpatient initiation of COVID-19-related therapies. Biomarker data encompassed pre-specified indices generally associated with adverse prognosis (e.g., high-sensitivity troponin I, C reactive protein, D-dimer, and white blood count). For patients with biomarkers obtained at multiple time points, peak values were used for study-related data analyses. ARDS was diagnosed based on the Berlin Definition.¹⁴ Accordingly, categories of ARDS were defined based on PaO₂/FiO₂ ratio: mild (200–300 mmHg), moderate (100–200 mmHg), and severe (<100 mmHg). DIC was defined according to the International Society on Thrombosis and Haemostasis (ISTH) diagnostic criteria by a 5-step diagnostic algorithm to calculate a score.¹⁵ Briefly, (1) the presence of clinical conditions known to be associated with DIC like a severe infection is a *conditio sine qua non* for the use of the algorithm; (2) the scoring system is based on a combination of several laboratory tests (D-dimer, prothrombin time, platelet count, and fibrinogen); (3) a DIC score equal or more than 5 is compatible with overt-DIC, whereas a score of less than 5 may be indicative for non-overt DIC.

2.3 | Standard echocardiography

Transthoracic echocardiography was performed in a standard manner with the same equipment (Vivid E95; GE Medical Systems, Milwaukee,

WI) by a single cardiologist (AM) with expertise in echocardiographic recording and interpretation, blinded to all clinical data. Images were obtained using a 3.5-MHz transducer in the parasternal and apical views (standard long-axis, two-, and four-chamber images), and measurements were performed after a 5-min run-in period for stabilization and equilibration. All included patients had at least fair image quality.

2.3.1 | Standard measurements

Cardiac chamber quantification was defined in accordance with consensus guidelines.¹⁶ As recommended, a dedicated RV-focused apical four-chamber view was used to measure the right ventricle. RV systolic function was evaluated using tricuspid annular plane excursion (TAPSE), fractional area change (FAC), and S' ; TAPSE was measured (on M-mode) as the distance of systolic excursion of the lateral tricuspid annulus along its longitudinal plane. FAC was obtained from the apical four-chamber view and is calculated as the difference in the end-diastolic area and the end-systolic area divided by the end-diastolic area. S' was measured on tissue Doppler as the peak tricuspid annular longitudinal velocity of excursion. Established cutoffs (TAPSE <17 mm, FAC <35%, S' <9.5 cm/sec) were used for each parameter. RV size was quantified based on end-diastolic diameter, which was measured at the RV base (septum-free wall) in apical 4-chamber orientation. RV dilation was defined using a binary cutoff (>4.1 cm). LV end-diastolic volume (LVEDVi), LV end-systolic volume (LVESVi), maximal LA volume (LAVi max) were measured from the apical two- and four-chamber views using the biplane modified Simpson rule and indexed to body surface area. LVEF was calculated as $(LVEDVi - LVESVi)/LVEDVi \times 100$. LV mass was quantified based on linear dimensions measured in parasternal long-axis. Pulmonary artery systolic pressure (PASP) was calculated based on tricuspid regurgitant velocity and inferior vena cava caliber. LV inflow was assessed using pulsed-wave Doppler by placing the sample volume at the level of mitral leaflet tips in the apical four-chamber view. The following measurements were obtained from the average of three consecutive beats: early diastolic flow peak velocity (E wave), late diastolic flow peak velocity (A wave), E/A velocity ratio, and E-wave deceleration time. Tissue Doppler Imaging (TDI) e' velocity was measured from the septal and lateral annulus in the apical four-chamber view. The average E/e' is calculated using the average value of both the septal and lateral TDI velocities.

2.3.2 | Speckle-tracking echocardiography

Speckle-tracking echocardiography (STE) analyses were conducted according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.¹⁷ All analyses were performed offline by a single experienced investigator (AM) using a commercially available semiautomated two-dimensional strain software (EchoPAC version 112; GE Medical Systems). Digital cine loops of two-dimensional grayscale RV images

were acquired in the RV-focused apical four-chamber view, during breath-hold with a stable electrocardiographic recording, and were stored for offline analysis. The frame rate was set between 60 and 80 frames per second as recommended to combine temporal resolution with adequate spatial definition and to enhance the feasibility of the frame-to-frame tracking technique. RV free wall endocardial border was traced in end-systole and the automatically generated region of interest was adjusted to exclude the pericardium. RVLS was calculated as the mean of the strain values in the three segments (basal, mid, and apical) of RV free wall (Figure 1). RVLS > -20% indicates RV systolic dysfunction.¹⁶

2.4 | Statistical methods

Continuous variables were expressed as mean \pm standard deviation (SD) or medians (interquartile range [IQR]), wherever appropriate. The independent samples *t*-test or Mann-Whitney *U*-test was used to compare normally and non-normally distributed data, respectively. Categorical variables were expressed as frequency number (%), and compared using Pearson's χ^2 test. Univariate and multivariate logistic regression analyses were used to evaluate the association of clinical variables with RV dysfunction quantified by RVLS. To prevent overfitting, variables included in the multivariate model were restricted to hypertension, smoker, diabetes, obesity, dyslipidemia, overt-DIC, severe ARDS, and invasive mechanical ventilation. A further multivariable regression model was added after adjusting for age and gender. Analyses were performed using SPSS statistical software, version 25.0 (SPSS, IBM). The significance level was set at .05.

3 | RESULTS

3.1 | Study population

Of 198 consecutive patients screened, 45 patients (mean age, 64.1 ± 12.0 years; 64.4% men) met the eligibility criteria during the study period. Demographics, clinical characteristics, and laboratory measurements are detailed in Table 1. Twenty-eight (62.2%) patients had a history of hypertension before COVID-19; 22 (48.9%) patients were obese; 10 (22.2%) patients were active smokers. The most common symptoms on admission were respiratory, followed by only fever, and diarrhea. The median time from illness onset to hospital admission was 7.2 days (IQR 5.1–10.4). Twelve (26.7%) patients met the criteria for severe ARDS. Almost half of the patients (22, 48.9%) required respiratory support with invasive mechanical ventilation. Appropriate therapy was administered according to the treatment guidelines. All patients had high-sensitivity cardiac troponin I (hs-cTnI) measurement during COVID-19 hospitalization, with a median peak value of 17.0 ng/L (IQR 10.0–50.4). Levels of D-dimer, C-reactive protein, and IL-6 were elevated. Sixteen (35.5%) patients matched the grade of overt-DIC (≥ 5 points) during the hospital stay. Discharged occurred after a median hospital length of stay of 25.2 days (IQR 16.3–34.8).

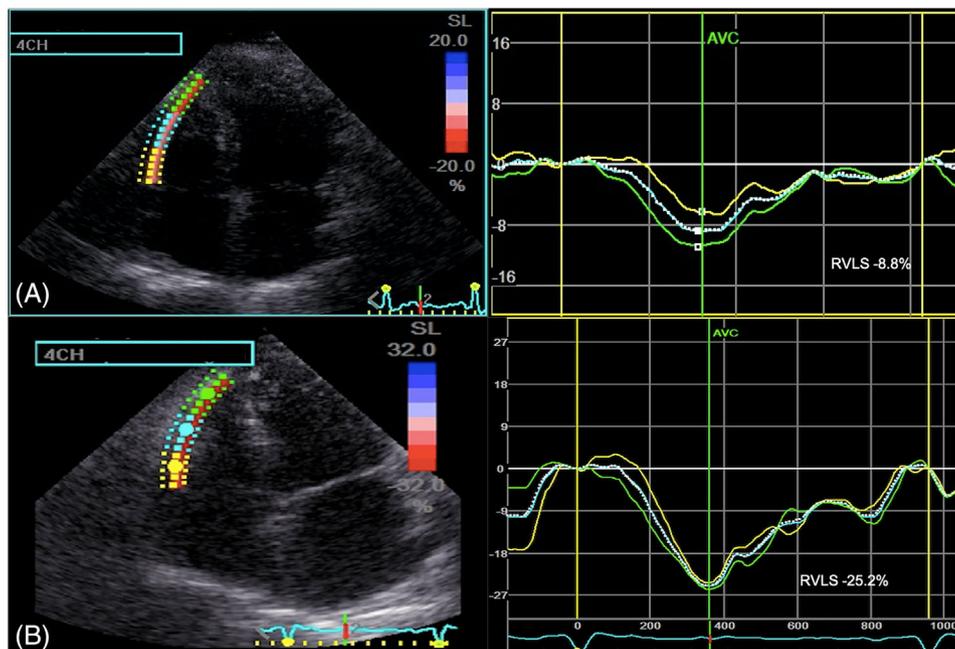


FIGURE 1 RVLS obtained from two-dimensional speckle tracking echocardiography in severe COVID-19 patient. Representative example of two-dimensional speckle tracking echocardiography-derived RVLS measurements from an apical four-chamber view. The free wall (FW) right ventricle is divided into three segments, basal FW (yellow), mid FW (light blue), apical FW (green). In the upper panel (A), an example of strain curves in a patient with impaired RVLS (-8.8%). In the lower panel (B), an example of strain curves in a patient with preserved RVLS (-25.2%). Abbreviation: AVC, Aortic valve closure.

3.2 | RV dysfunction detected at follow-up

All 45 patients referred for transthoracic echocardiography 6-months after discharge were alive with no re-hospitalization for any cause. We divided our study population into two groups according to the RVLS abnormality threshold: 19 patients (42.2%) with normal RVLS (group A), 26 patients (57.8%) with pathological RVLS (group B). As shown in Table 2, patients in group A had similar LV volumes (mean LVEDVi, 46.3 ± 9.3 vs. 47.0 ± 10.3 ml/m², $p = .829$; mean LVESVi, 18.1 ± 5.3 vs. 20.4 ± 5.6 ml/m², $p = .190$), and LVEF (60.7 ± 4.7 vs. $56.7 \pm 5.6\%$, $p = .147$) compared with those in group B. Both groups did not exhibit significant differences with respect to LA size and LV mass (all $p = ns$). Abnormal diastolic function (E/A, E/e') was slightly more common among patients in group B. TAPSE and S' was lower in group B than in group A (21.4 ± 4.3 vs. 18.4 ± 4.2 mm, $p = .027$; 12.6 ± 2.4 vs. 11.1 ± 2.0 cm/sec, $p = .044$). While FAC, RV dimension, and PASP did not differ between the two groups (all $p = ns$). Regarding clinical characteristics, there were no significant differences in age, gender, comorbidities, lymphocyte count, hs-TnI, D-dimer, prothrombin time, platelet count, fibrinogen, and respiratory parameters. Conversely, the DIC score was significantly higher in group B than in group A ($4.8 \pm .5$ vs. $3.6 \pm .6$, $p = .03$). The risk of sustained RV dysfunction increased the higher the DIC score was, being approximately two times greater for patients with overt-DIC than for those with non-overt DIC (46.2 vs. 21.1% , $p = .03$). As shown in Figure 2, categories of ARDS did not modulate the interaction between DIC score and RVLS. The curve begins to rise toward worse RVLS for DIC score values above 4, with a fast and steady

increase from lower to higher DIC score values regardless of the ARDS severity. In the multivariate logistic regression model, overt-DIC was the only independent predictor of sustained RV dysfunction (OR 1.233, 95% CI 1.041–1.934, $p = .043$). This result was confirmed in the same model adjusted for age and gender (Table 3).

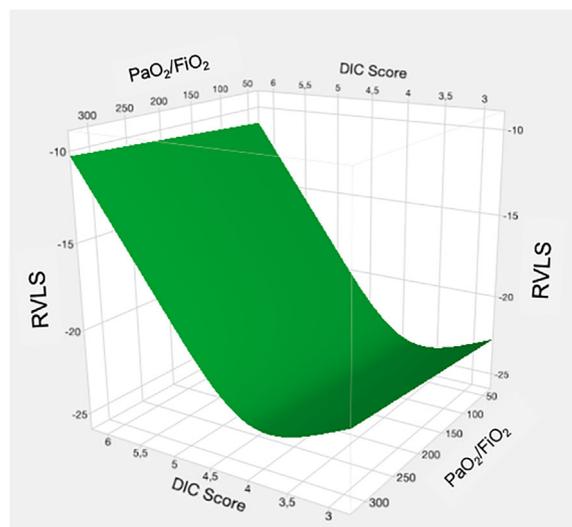


FIGURE 2 Relationship between right ventricular longitudinal strain, DIC Score, and PaO₂/FiO₂. Interaction between right ventricular longitudinal strain and DIC score as PaO₂/FiO₂ varies.

TABLE 1 Characteristics of patients with severe COVID-19

Variables	All population (n = 45)
Demographic characteristics	
Age, years	64.1 ± 12.0
Male, n (%)	29 (64.4)
Body mass index, kg/m ²	31.0 ± 5.9
Smoker, n (%)	10 (22.2)
Hypertension, n (%)	28 (62.2)
Diabetes, n (%)	7 (15.6)
Obesity, n (%)	22 (48.9)
Dislipidemia, n (%)	13 (28.9)
Symptoms	
Fever, n (%)	39 (86.7)
Dyspnea, n (%)	37 (82.2)
Dry cough, n (%)	32 (71.1)
Diarrhea, n (%)	7 (15.6)
Time from illness onset to hospital admission, days	7.2 (5.1–10.4)
Hospital length of stay, days	25.2 (16.3–34.8)
Laboratory findings (peak)	
WBC count, ×10 ⁹ /ml	7.0 (4.8–9.4)
hs-Tnl, ng/L	17.0 (10.0–50.4)
CRP, mg/L	16.1 (9.4–25.5)
PLT count, ×10 ⁹ /ml	200 (141–260)
PT time, s	18.9 (17.5–21.4)
IL-6, pg/ml	276 (169–1097)
D-dimer, ng/mL	2017 (1100–7423)
Fibrinogen, g/L	98 (50–272)
DIC score	4.0 ± .8
Overt-DIC, n (%)	16 (35.5)
Respiratory parameters	
PaO ₂ /FiO ₂ ratio peak, mmHg	188.7 (96.5–252.1)
Severe ARDS, n (%)	12 (26.7)
IMV, n (%)	22 (48.9)
Duration of the ventilation, days	10.7 (5.1–16.3)

Data are mean ± SD, n (%), or median (IQR).

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; hs-Tnl, high-sensitivity troponin I; IL-6, interleukin-6; IMV, invasive mechanical ventilation; IQR, interquartile range; PaO₂/FiO₂, arterial oxygen partial pressure to fractional inspired oxygen; PLT, platelet; PT, prothrombin time; SD, standard deviation; WBC, white blood cells.

4 | DISCUSSION

The present study shows there is a high rate of sustained RV dysfunction in patients recovering from severe COVID-19. None of the 45 patients included in this analysis had history of cardiac disease. How-

ever, 26 of 45 patients showed impaired RVLS derived from 2D-STE at 6-months' follow-up. The presence of echocardiographic abnormalities in otherwise healthy subjects suggests cardiac dysfunction as a lasting consequence of SARS-CoV-2 infection. Of note, patients with higher DIC scores were more likely to have a worse RV impairment 6-months after discharge. Moreover, overt-DIC emerges as the only independent predictor of sustained RV dysfunction in this clinical setting.

4.1 | Sustained RV dysfunction

The acute effect of COVID-19 on RV activity has recently been much debated. Because the right ventricle mainly acts as a passive conduit in cardiac functioning, it is easily affected by a slight increase in pulmonary vascular resistance.¹⁸ It seems that the pathophysiological pathways of COVID-19 including increased RV afterload after ARDS and pulmonary embolism are possible mechanisms for RV dysfunction in COVID-19 patients.¹⁹ Emerging evidence suggests that acute RV involvement is common in patients hospitalized with COVID-19 and was frequently in those with more severe types. RV contractile dysfunction appeared to occur after geometric remodeling, with RV dysfunction present in less than one-quarter of inpatients with RV dilation.⁵ Conversely, the long-term RV sequelae of COVID-19 have not been fully explored yet. Sustained RV cardiac involvement was found using magnetic resonance imaging in a subgroup of patients recovered from COVID-19; however, most included patients had mild- or moderate-type previously.⁸ The present study is the first to show the sustained RV impairment by STE in patients recovering from a severe type of COVID-19. Whereas RV dysfunction was present in more than half of our population, RV dilation rarely occurred at 6-months follow-up. RV dilation is frequent in hospitalized patients with COVID-19 infection.²⁰ It likely depends on multifactorial mechanisms includes thrombotic events, hypoxemic vasoconstriction, cytokine milieu, and direct viral damage. We can only speculate on the nature of our findings, but we conclude that dilation is an early response of the thin-walled right ventricle to acute and temporary increased afterload; instead, RV dysfunction is sustained damage concerning RV myocyte loss due to lasting detrimental effect. We have provided no evidence to support that RV dysfunction is permanent. It is also possible that the recovery of RV systolic function is a slow process. Future studies are warranted to clarify that statement.

4.2 | Role of DIC

Although COVID-19 is primary a respiratory illness, emerging data show that severe form can progress to a more critical and systemic disease, characterized by coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as DIC.^{10,11} Therefore, coagulation tests should be considered useful in severe cases of COVID-19. A consistent observation among patients with severe COVID-19 is an elevation of D-dimer in the peripheral blood. In comparison with classic bacterial-sepsis-associated

TABLE 2 Characteristics of patients with severe COVID-19 according to RVLS abnormality threshold

Variables	RVLS \leq -20 (n = 19)	RVLS > -20 (n = 26)	p value
Demographic and clinical characteristics			
Age, years	65.4 \pm 12.9	63.2 \pm 11.4	.53
Male, n (%)	5 (26.3)	11 (42.3)	.27
Body mass index, kg/m ²	30.4 \pm 5.0	31.4 \pm 6.6	.58
Smoker, n (%)	4 (21.1)	6 (23.1)	.87
Hospital length of stay, days	21.5 (14.3–29.7)	30.5 (16.0–36.5)	.18
Comorbidities			
Hypertension, n (%)	11 (57.9)	17 (65.4)	.61
Diabetes, n (%)	4 (21.1)	3 (11.5)	.38
Obesity, n (%)	12 (63.2)	10 (38.5)	.10
Dislipidemia, n (%)	7 (36.8)	6 (23.1)	.31
Laboratory findings (peak)			
WBC count, $\times 10^9$ /L	5.6 (3.7–9.1)	7.5 (5.7–9.8)	.14
hs-Tnl, ng/L	20.0 (10.0–50.4)	16 (8.8–43.7)	.46
CRP, mg/L	14.2 (3.0–26.5)	19.7 (13.3–24.9)	.18
PLT count, $\times 10^9$ /L	219 (137–283)	200 (145–232)	.33
PT time, s	17.9 (15.4–20.7)	19.5 (17.5–21.4)	.13
IL-6, pg/ml	919 (143–1209)	199 (188–559)	.80
D-dimer, ng/mL	2024 (1600–6498)	2010 (1050–8447)	.90
Fibrinogen, g/L	43 (10–263)	54 (14–313)	.88
DIC score	3.6 \pm .6	4.8 \pm .5	.03
Overt-DIC, n (%)	4 (21.1)	12 (46.2)	.03
Respiratory parameters			
PaO ₂ /FiO ₂ ratio peak, mmHg	214.7 (110.6–263.9)	188.8 (91.6–250.1)	.54
Severe ARDS, n (%)	4 (21.1)	8 (30.8)	.47
IMV, n (%)	8 (42.1)	14 (53.8)	.44
Duration of the ventilation, days	10.5 (7.2–14.9)	10.2 (5.0–19.5)	.16
Echocardiographic data on follow-up			
LVEDVi, ml/m ²	46.3 \pm 9.3	47.0 \pm 10.3	.83
LVESVi, ml/m ²	18.1 \pm 5.3	20.4 \pm 5.6	.19
LVEF, %	60.7 \pm 4.7	56.7 \pm 5.6	.15
LAVi max, ml/m ²	30.6 \pm 10.9	30.8 \pm 11.5	.95
LV mass, gr/m ²	73.5 \pm 20.5	66.8 \pm 11.0	.18
E/A velocity ratio	1.1 \pm .3	.9 \pm .3	.09
E/e' ratio	7.9 \pm 2.9	10.2 \pm 4.6	.06
TAPSE, mm	21.4 \pm 4.3	18.4 \pm 4.2	.03
RVFAC, %	41.6 \pm 8.7	38.8 \pm 11.0	.37
S', cm/sec	12.6 \pm 2.4	11.1 \pm 2.0	.04
RV diameter, mm	36.0 \pm 3.9	37.8 \pm 6.9	.32
PASP, mmHg	10.8 \pm 7.8	13.8 \pm 9.2	.25

Data are mean \pm SD, n (%), or median (IQR).

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; hs-Tnl, high-sensitivity troponin I; IL-6, interleukin-6; IMV, invasive mechanical ventilation; IQR, interquartile range; PaO₂/FiO₂, arterial oxygen partial pressure to fractional inspired oxygen; PLT, platelet; PT, prothrombin time; SD, standard deviation; WBC, white blood cells.

Echocardiographic data: RVFAC, right ventricular fractional area change; LAVi, indexed left atrial volume; LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; RV, right ventricular; RVLS, right ventricular longitudinal strain; TAPSE, tricuspid annular plane systolic excursion. $p < .05$ was considered statistically significant.

TABLE 3 Multivariate logistic regression models for predictors of RV dysfunction

Variables	Unadjusted			Adjusted for age and gender		
	Odds ratio	95% CI	<i>p</i> value	Odds ratio	95% CI	<i>p</i> value
Smoker	1.500	.423–5.315	.530	1.501	.313–7.191	.611
Hypertension	1.545	.724–3.299	.361	1.137	.921–5.685	.368
Diabetes	.750	.168–3.351	.170	.899	.233–3.990	.233
Obesity	.833	.360–1.929	.267	.446	.101–1.996	.286
Overt-DIC	1.233	1.041–1.934	.043	1.178	1.037–1.997	.049
Severe ARDS	1.943	.602–6.642	.258	1.567	.569–7.456	.354
IMV	1.765	.734–4.172	.207	2.134	.677–6.724	.195

Abbreviations: ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; IMV, invasive mechanical ventilation. $p < .05$ was considered statistically significant.

coagulopathy, a relatively modest decrease in platelet count and a prolongation of the prothrombin time are reported, as well as mean fibrinogen concentrations are at the upper limits of normal.^{21,22} Our results are supportive of the previous report, confirming the increased D-dimer concentration as the most typical finding. CAC is characterized in a majority of cases by a proclivity for venous, arterial, and microvascular thrombosis. Previous autopsy series of patients who died for COVID-19 showed the presence of diffuse microvascular thrombosis in the lungs, defined as pathological occlusion of microvessels (arterioles, capillaries, and venules) by platelet- and/or fibrin-rich thrombi, whereas the hallmarks of classic ARDS with diffuse alveolar damage and hyaline membranes were not prominent.^{23,24} In summary, available evidence suggests that CAC is a combination of various-grade DIC and localized pulmonary microvascular thrombosis, which could have a substantial impact on organ dysfunction in critical patients, primarily on the right ventricle. Some authors reported novelties about the prognostic value of DIC in patients hospitalized with COVID-19. Tang et al. showed abnormal coagulation parameters and poor prognosis in 183 consecutive patients: most of the non-survivors matched the grade of overt-DIC.²⁵ However, data on the long-term role of DIC in patients who survive their illness are lacking. To the best of our knowledge, this is the first study to comprehensively show the DIC-related sustained RV dysfunction risk in patients recovered from severe COVID-19. Of note, categories of ARDS did not show a multiplicative effect on the dismal outcome carried by DIC in this clinical setting, casting doubts on its role in this process. Based on our in-depth analysis, we do not feel to totally exclude an effect of ARDS on the RV function. Larger studies adequately powered for the interaction between these variables are needed.

4.3 | Clinical impact

Selecting patients who have survived from COVID-19 in need of close monitoring is still challenging. Guidelines suggesting how to follow up on these patients are not available yet. Hence, further risk stratification tools are needed. Our study results, showing the high incidence of sustained RV dysfunction through the use of 2D-STE in patients recovered

from severe COVID-19, highlight the key role of this newer imaging technique, in order to set the best strategies. Future studies are needed to verify the clinical and prognostic value of sustained RV dysfunction in recovered COVID-19 patients. Moreover, we identified overt-DIC as an independent predictor of sustained RV dysfunction, strengthening the in-hospital monitoring of coagulation biomarkers to calculate the DIC score, firstly in patients with severe-type.

4.4 | Study limitations

The main limitation of this report is the relatively small, single-center cohort studied. However, the inclusion criteria were quite selective, limiting the eligibility for this study. Almost half of the screened patients were excluded because they had known cardiopathy, as it would have hampered data interpretation because of heterogeneity. Thus, larger studies adequately powered are warranted to confirm our results. Secondly, our cohort was retrospectively identified but all measurements were performed prospectively and retrieved unaltered. Thus, our results are highly applicable to clinical practice. Lastly, our findings would have been more relevant if RV dysfunction had been confirmed by advanced cardiac imaging, as well as associated with increased pulmonary vascular resistance.

5 | CONCLUSION

Sustained RV impairment frequently occurs in patients recovered from severe COVID-19. Whether it may be helpful for risk stratification is uncertain, and needs to be further investigated. Our findings provide new insight on the role of the DIC, showing its value as an independent predictor of sustained dysfunction assessed by the recent application of speckle-tracking echocardiography to the right ventricle.

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CONFLICT OF INTEREST

All authors have no conflict of interest.

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REFERENCES

- Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Inf Dis*. 2020; 20:533-534.
- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020; 323:1061-1069.
- Biagi A, Rossi L, Malagoli A, et al. Clinical and epidemiological characteristics of 320 deceased patients with COVID-19 in an Italian Province: a retrospective observational study *J Med Virol*. 2020; 92:2718-2724.
- Szekely Y, Lichter Y, Taieb P, et al. Spectrum of cardiac manifestations in COVID-19: a systematic echocardiographic study. *Circulation*. 2020; 142:342-353.
- Kim J, Volodarskiy A, Sultana R, et al. Prognostic utility of right ventricular remodeling over conventional risk stratification in patients with COVID-19. *J Am Coll Cardiol*. 2020; 76:1965-1977.
- Dweck MR, Bularga A, Hahn RT, et al. Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging*. 2020;21:949-958.
- Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:1265-1273
- Huang L, Zhao P, Tang D, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging*. 2020;13:2330-2339.
- Longobardo L, Suma V, Jain R, et al. Role of two-dimensionale speckle-tracking echocardiography strain in the assessment of right ventricular systolic function and comparison with conventional parameters. *J Am Soc Echocardiogr*. 2017;30:937-946.
- Li Y, Li H, Zhu S, et al. Prognostic value of right ventricular longitudinal strain in patients with COVID-19. *JACC Cardiovasc Imaging*. 2020;13:2287-2299.
- Becker RC. COVID-19 update: Covid-19-associated coagulopathy. *J Thromb Thrombolysis*. 2020;50:54-67.
- Levi M, Thachil J, Iba T, Levy J. Coagulation abnormalities and thrombosis in patients with COVID-19 infection. *Lancet Haematol*. 2020;7:e438-e440.
- WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. January 28, 2020. Accessed March 1, 2020.
- Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307:2526-2533.
- Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86:1327-1330.
- 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. *J Am Soc Echocardiogr*. 2015;28:1-39.
- Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr*. 2011;12:167-205.
- Repešš X, Charron C, Vieillard-Baron A. Right ventricular failure in acute lung injury and acute respiratory distress syndrome. *Minerva Anesthesiol*. 2012;78:941-8.
- Park JF, Banerjee S, Umar S. In the eye of the storm: the right ventricle in COVID-19. *Pulm Circ*. 2020;10:2045894020936660.
- Argulian E, Sud K, Vogel B, et al. Right ventricular dilation in hospitalized patients with COVID-19 infection *JACC Cardiovasc Imaging*. 2020;13:2459-2461.
- Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708-1720.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.
- Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med*. 2020;8:681-686.
- Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. 2020;220:1-13.
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18:844-847.

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