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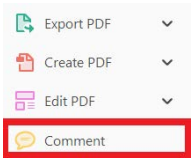

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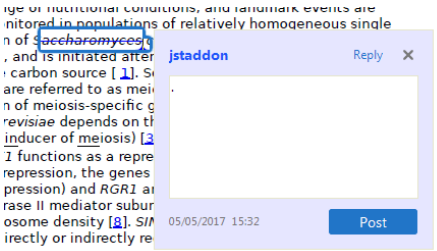

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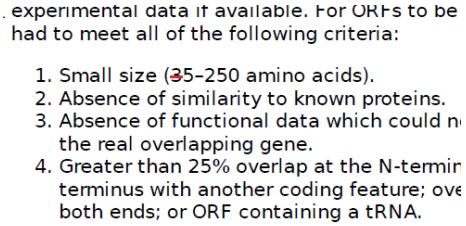

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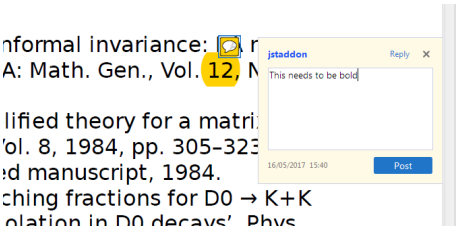

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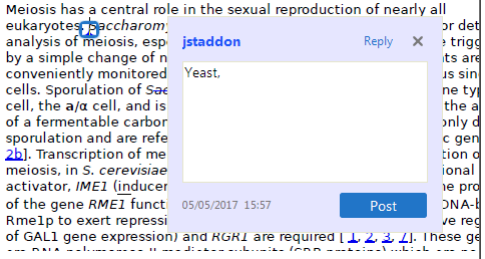

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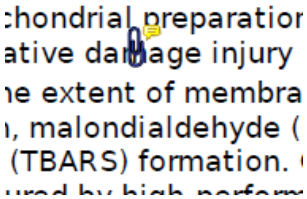

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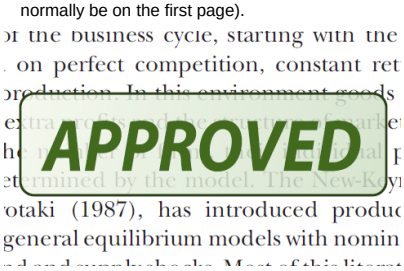

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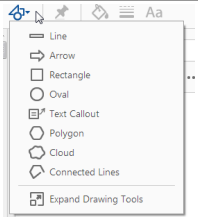

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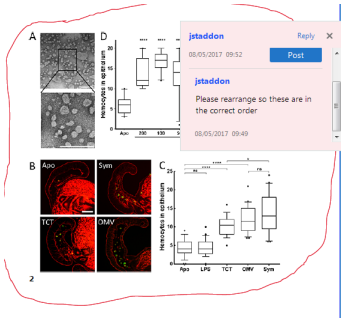

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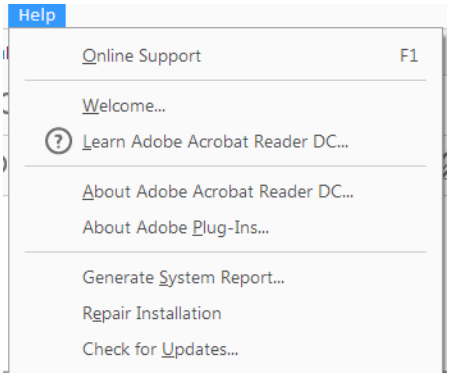

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Journal of the American Heart Association

ORIGINAL RESEARCH

Pericardial Involvement in Hospitalized Patients With COVID-19: Prevalence, Associates, and Clinical Implications

Eihab Ghantous, MD*; Yishay Szekely, MD*; Yael Lichter, MD; Erez Levi, MD; Philippe Taieb, MD; Ariel Banai, MD; Orly Sapir, MD; Yoav Granot, MD; Lior Lupu, MD; Aviram Hochstadt, MD; Ilan Merdler, MD, MHA; Ariel Borohovitz, MD; Sapir Sadon, MS; Merav Ingbir, MD; Michal Laufer-Perl, MD; Shmuel Banai, MD; Yan Topilsky, MD

BACKGROUND: The scope of pericardial involvement in COVID-19 infection is unknown. We aimed to evaluate the prevalence, associates, and clinical impact of pericardial involvement in hospitalized patients with COVID-19.

METHODS AND RESULTS: Consecutive patients with COVID-19 underwent clinical and echocardiographic examination, irrespective of clinical indication, within 48 hours as part of a prospective predefined protocol. Protocol included clinical symptoms and signs suggestive of pericarditis, calculation of modified early warning score, ECG and echocardiographic assessment for pericardial effusion, left and right ventricular systolic and diastolic function, and hemodynamics. We identified predictors of mortality and assessed the adjunctive value of pericardial effusion on top of clinical and echocardiographic parameters. The study included 530 patients. Pericardial effusion was found in 75 (14%), but only 17 patients (3.2%) fulfilled the criteria for acute pericarditis. Pericardial effusion was independently associated with modified early warning score, brain natriuretic peptide, and right ventricular function. It was associated with excess mortality (hazard ratio [HR], 2.44; P=0.0005) in nonadjusted analysis. In multivariate analysis adjusted for modified early warning score and echocardiographic and hemodynamic parameters, it was marginally associated with mortality (HR, 1.86; P=0.06) and improvement in the model fit (P=0.07). Combined assessment for pericardial effusion with modified early warning score, left ventricular ejection fraction, and tricuspid annular plane systolic excursion was an independent predictor of outcome (HR, 1.86; P=0.02) and improved model fit (P=0.02).

CONCLUSIONS: In hospitalized patients with COVID-19, pericardial effusion is prevalent, but rarely attributable to acute pericarditis. It is associated with myocardial dysfunction and mortality. A limited echocardiographic examination, including left ventricular ejection fraction, tricuspid annular plane systolic excursion, and assessment for pericardial effusion, can contribute to outcome prediction.

Key Words: acute pericarditis ■ COVID-19 ■ echocardiography ■ pericardial effusion

COVID-19 infection has a wide range of disease severity, from asymptomatic or mild, self-limiting illness to severe progressive pneumonia, multiorgan failure, and death.[1,2] Reports suggest that cardiac complications are common and are associated with increased mortality.[3,4] We have previously shown that the most common cardiac manifestation in consecutive hospitalized patients with COVID-19 infection is right ventricular (RV) dysfunction or dilatation (39%), followed by left ventricular (LV) diastolic dysfunction (16%) and systolic dysfunction (10%).[5] A recent report evaluated the incidence of cardiac manifestations in a large

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CLINICAL PERSPECTIVE

What Is New?

- Although acute pericarditis is infrequent among hospitalized patients with COVID-19, pericardial effusion is common and associated with myocardial dysfunction and excess mortality.

What Are the Clinical Implications?

- Clinicians taking care of patients with COVID-19 can use a limited echocardiographic examination for risk stratification, including left ventricular ejection fraction, tricuspid annular plane systolic excursion, and the presence of pericardial effusion.

Nonstandard Abbreviations and Acronyms

MEWS	modified early warning score
TAPSE	tricuspid annular plane systolic excursion

group of consecutive patients with acute COVID-19 infection, excluding patients with previous cardiovascular disease. Systolic dysfunction based on low ejection fraction occurred in 3.4%, but in 24% when based on abnormal longitudinal strain. Diastolic dysfunction occurred in 20%, and RV systolic dysfunction was noted in 18%.[6] Cardiac monitoring using clinical, laboratory, and imaging parameters can be used to help risk stratify patients with COVID-19.[2,5,7] However, most reports on cardiac involvement focus on myocardial involvement, and reports describing pericardial disease are less common, mostly retrospective or based on systematic literature review, assessing only patients with clinically indicated echocardiographic examinations.[6,8–20] More important, none of these reports used a prospectively defined echocardiographic protocol. We sought to define the prevalence and associates of pericardial involvement in consecutive COVID-19 hospitalized patients of all disease grades, who underwent a prospectively predefined comprehensive echocardiographic evaluation, and to determine its prognostic effect.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. We prospectively studied consecutive adult patients (aged ≥18 years) admitted between March 21, 2020, and September 16, 2020, to the Tel Aviv Medical Center because of COVID-19 infection. All patients had a diagnosis of COVID-19 infection confirmed by a positive reverse-transcriptase polymerase chain reaction assay. Demographic data, comorbid conditions, medications, physical examination, laboratory, and ECG findings were systematically recorded. Patients were risk stratified according to their COVID-19 modified early warning score (MEWS). MEWS is predictive of the need for invasive mechanical ventilation and mortality among patients with COVID-19.[5,21,22] All patients underwent comprehensive transthoracic echocardiography within 48 hours of admission as part of a predefined step-by-step protocol. Clinical and imaging data were collected prospectively, including the presence or absence of pericardial effusion. For the diagnosis of pericarditis, we used the European Society of Cardiology guidelines for diagnosis and management of pericardial disease based on at least 2 of the 4 criteria of: pericardial chest pain, pericardial rub, new widespread ST-segment elevation or PR depression on ECG, and pericardial effusion (new or worsening).[23] Mortality analysis started at time of baseline echocardiographic examination and included in-hospital mortality. Mortality was ascertained until the end of follow up, beyond hospitalization and irrespective of discharge date, for all patients, by telephone calls, and was complete for all the patients. The ethics committee of the Tel Aviv Medical Center approved the study (institutional review board number 0196-20-TLV) and voided the requirement of informed consent for the echocardiographic assessment.

Echocardiography

Echocardiography was performed in a standard manner with the same equipment (CX 50; Philips Medical Systems, Bothell, WA) by cardiologists with expertise in echocardiographic recording and interpretation. In accordance with current guidelines,[24] the following measures were undertaken to minimize the risk of infection: (1) All echocardiographic studies were bedside studies performed at the designated COVID-19 intensive care or internal ward units. (2) All echocardiographic examinations were performed with small, dedicated scanners because of their easier disinfection. (3) Echocardiographic scanners were set aside in each COVID-19–designated ward to minimize the risk of infection spread. (4) Personal protection at the time of echocardiographic recordings included N-95 respirator masks, fluid-resistant gowns, gloves, head covers, and eye shields. (5) Electrocardiographic monitoring during imaging was omitted, and all measurements were performed offline to reduce exposure and contamination. LV diameters, ejection fraction, and mass were measured as recommended.[25] Measurements of mitral inflow included the peak early filling (E wave) and late diastolic filling (A wave) velocities, E/A ratio, and deceleration time of early filling velocity. Early diastolic mitral septal and

lateral annular velocities (e′) were measured in the apical 4-chamber view.[26] Left atrial volume was calculated with the biplane area-length method at end systole. Forward stroke volume was calculated from the LV outflow tract with subsequent calculation of cardiac output.

From 4-chamber views encompassing the entire RV, end-systolic and end-diastolic RV areas and tricuspid annulus were measured. RV function was evaluated by tricuspid annular plane systolic excursion (TAPSE), systolic tricuspid lateral annular velocity measured in the apical 4-chamber view, and fractional area change.[25,27] Hemodynamic right-sided assessment included the measurement of the pulmonic flow acceleration time to assess pulmonary vascular resistance.[28]

Statistical Analysis

Continuous normally distributed parameters were presented as means±SD and compared using the Student *t* test. Nonnormally distributed data were presented by median and first and third quartiles and compared using the Wilcoxon rank-sum test. Normality was assessed using the Shapiro-Wilk test and visual inspection of quantile-quantile plots. Categorical data were compared between groups using the χ^2 test or Fisher exact test, and expressed as numbers and/or percentages. To analyze the association of pericardial effusion with clinical and cardiac findings, we first performed binary logistic regression univariate analyses with clinical, laboratory, and echocardiographic parameters as independent variables and presence of pericardial effusion as dependent variable. For the multivariable analysis, in the first step, all the variables with significant univariate association with pericardial effusion ($P<0.05$) were grouped into clinical, laboratory, and LV and RV parameters, because many were significantly correlated. In the second step, we assessed correlations between the selected variables within each group to avoid collinearity ($R^2>0.7$; $P<0.0001$). If any such pairs were found, one of the predictor variables was selected for inclusion in the final analysis and the other was ignored. The variable with the lowest *P* value was chosen to be included in the final multivariable analysis. To assess if pericardial effusion is independently associated with mortality, we used multivariable Cox proportional hazard models, allowing calculation of adjusted hazard ratio (HR). We first performed univariate Cox hazard analyses with clinical, laboratory, and echocardiographic parameters as independent variables and mortality as dependent variable. For the multivariable analysis, in the first step, all the variables with significant univariate association with mortality ($P<0.05$) were grouped into clinical, laboratory, and LV and RV parameters, because many were significantly correlated. In the second step to detect multicollinearity, we used correlation factor analyses to determine if any pairs of predictor variables were highly correlated (correlation coefficients >0.7) and therefore likely to result in multicollinearity. If any such pairs were found, one of the predictor variables was selected for inclusion in the final analysis and the other was ignored. The variable with the lowest *P* value was chosen to be included in the final Cox hazard multivariable analysis. Time of follow-up was calculated between baseline echocardiography and death, or last date of follow-up. Analysis for survival was obtained for all patients. The survival estimate was calculated using the Kaplan-Meier method and compared by log-rank test. Different multivariable nested models were compared with regard to their model fit by computing a χ^2 difference test. All data were analyzed with the JMP System software version 14.0 (SAS Institute, Inc, Cary, NC). All authors participated in designing the study, collecting and analyzing data, and drafting and revising the article.

RESULTS

Prevalence of Pericardial Effusion and Pericarditis

Clinical data were collected for 664 consecutive patients hospitalized with COVID-19 infection. A total of 134 patients were excluded because they did not undergo echocardiographic assessment (35 were discharged within 48 hours of admission, 4 patients refused, 80 patients had a "do not intubate/resuscitate" status and received palliative care, and 15 patients died within 48 hours from admission). The patient flowchart is shown in Figure 1.

The final study group included 530 patients (aged 63.1±18.3 years; 62% men) who underwent clinical and echocardiographic evaluation. At the time of the baseline evaluation, all patients had COVID-19 symptoms, and were stratified according to mild/moderate disease (oxygen saturation ≥94% in room air) in 278 (52%), severe disease (need for oxygen supplement) in 233 (44%), and critical disease (need for mechanical ventilation or use of vasopressors and/or extracorporeal life support) in 19 (4%). Of these patients, 75 (14.2%) had pericardial effusion. Pericardial effusion was mild in 72 patients, and moderate in 3 patients. None of the patients in our cohort required pericardial drainage. Only 17 of 75 (22.7%) of the patients with pericardial effusion fulfilled the definition criteria for pericarditis, based on the combination of typical ECG changes (7 patients) and/or typical chest pain (12 patients). There were no patients without pericardial effusion who fulfilled the definition criteria for pericarditis.

Association of Pericardial Effusion With Clinical and Echocardiographic Parameters

Baseline demographic, clinical, and echocardiographic parameters, stratified by patients with or without

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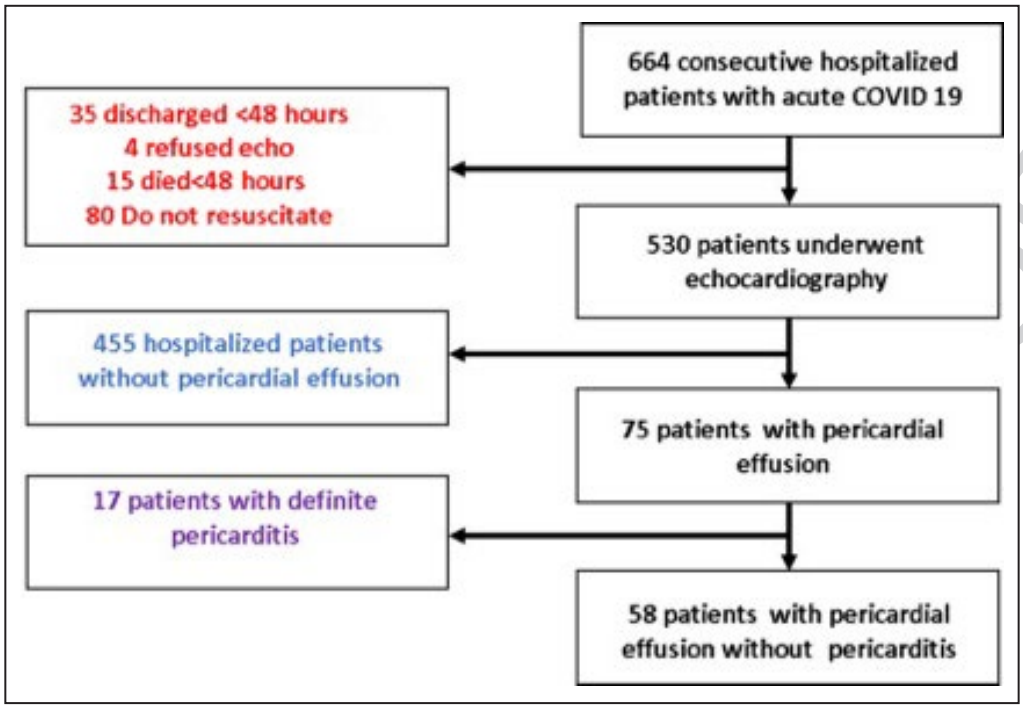

Figure 1. Flowchart showing patient selection for the final cohort.

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pericardial effusion, are shown in Table 1. Patients with pericardial effusion were older, had worse disease severity, had higher MEWS, had higher brain natriuretic peptide (BNP), and had lower hemoglobin, but did not differ in levels of troponin-I or CRP (C-reactive protein). They also had higher prevalence of ischemic heart disease, hypertension, and atrial fibrillation. Patients with pericardial effusion had poorer RV echocardiographic functional parameters (TAPSE and systolic tricuspid lateral annular velocity), lower cardiac index, higher E/e', higher estimated right atrial pressure, and higher pulmonary vascular resistance. Table 2 shows the odds ratio (OR) of univariate and multivariate analysis for association of pericardial effusion with clinical and echocardiographic parameters. The final univariate and multivariate parameters entered into the model are described under the headings "Univariate analysis OR" and "Multivariable analysis OR." These analyses suggest that pericardial effusion is independently associated with worse MEWS, higher BNP, and poorer RV function. Table S1 shows the main echocardiographic findings categorized by COVID-19 severity (mild/moderate versus severe and critical).

Association of Pericardial Effusion With All-Cause Mortality

There were 97 deaths (18.3%) among the 530 patients who underwent echocardiography. All-cause mortality was higher in patients with pericardial effusion (25/75 [33.3%] versus 72/455 [15.8%]; P=0.0007). Kaplan-Mayer analysis for overall survival, stratified by the presence of pericardial effusion, is shown in Figure 2. Univariate associates of mortality are shown in Table S2. Clinical parameters associated with mortality were age, MEWS, troponin-I, and BNP. LV echocardiographic parameters associated with mortality included LV ejection fraction (LVEF), stroke volume index, and E/e'. RV echocardiographic parameters associated with mortality included RV end-systolic area, TAPSE and systolic tricuspid lateral annular velocity, right atrial pressure, and shorter pulmonic acceleration time. Multivariate associates of mortality are shown in Table 3. The final univariate and multivariate parameters entered into the Cox hazard model are described under the headings "Univariate analysis HR" and "Multivariable analysis HR." In multivariate analysis adjusted for echocardiographic and hemodynamic parameters, pericardial effusion was marginally associated with mortality (HR, 1.83 [95% CI, 0.95–3.4]; P=0.06), and improved the model fit in nested model (P=0.05 for χ^2 difference test). In multivariate analysis adjusted for echocardiographic variables, hemodynamic parameters, and MEWS, pericardial effusion was marginally associated with mortality (HR, 1.86 [95% CI, 0.95–3.5]; P=0.06), and marginally improved the model fit in nested model (P=0.07 for χ^2 difference test). In multivariate analysis adjusted for significant clinical parameters, echocardiographic variables,

Table 1. Baseline Characteristics Stratified by the Presence or Absence of Pericardial Effusion

Variables	Pericardial effusion (n=75)	Without pericardial effusion (n=455)	*P* value
Clinical characteristics			
Age, mean±SD, y	69.1±16.4	62.4±17.6	0.001
Male sex, n (%)	40 (53.3)	287 (63.08)	0.12
Disease severity, n (%)			0.09
Mild/moderate	39 (52)	239 (53)	0.03
Severe	29 (39)	204 (45)	
Critical	7 (9)	12 (2)	
Modified early warning score, mean±SD	6.0±3.6	4.3±3.4	0.001
Body mass index, mean±SD, kg/m^2	27.6±5.6	27.3±5.8	0.69
Ischemic heart disease, n (%)	21 (28)	65 (14.2)	0.005
Stroke, n (%)	9 (12)	38 (8.4)	0.28
Chronic kidney disease, n (%)	12 (16)	43 (9.45)	0.1
Diabetes, n (%)	30 (40)	137 (30.1)	0.1
Hypertension, n (%)	49 (65.3)	202 (44.4)	0.001
Thyroid disease, n (%)	4 (5.3)	10 (2.2)	0.12
Autoimmune diseases, n (%)	4 (5.3)	29 (6.3)	0.73
Temperature, mean±SD, ° C	37.45±0.99	37.51±0.9	0.59
Respiratory rate, mean±SD, breaths/min	17.6±10.2	20.14±5.63	0.72
O_2 saturation, mean±SD, %	92.08±10.13	93.22±7.22	0.36
Heart rate, mean±SD, beats/min	74.1±15.9	77.2±14.8	0.12
Systolic blood pressure, mean±SD, mm Hg	135.94±24.1	135.46±31.08	0.87
Diastolic blood pressure, mean±SD, mm Hg	71.72±13.83	76.95±13.15	0.003
Hemoglobin, mean±SD, g/dL	12.5±2.43	13.33±1.9	0.006
White blood cells, mean±SD, 10^3/µL	8.33±5.54	8.2±13.04	0.88
Platelets, mean±SD, 10^3/µL	216.75±95.89	203±59±81.84	0.26
Blood urea nitrogen, mean±SD, mg/dL	26.21±24.66	20.86±16.42	0.077
Thyroid-stimulating hormone, mean±SD, µIU/mL	3.3±8.1	1.9±5.5	0.19
Free thyroxine, mean±SD, ng/dL	1.2±0.3	1.2±0.3	0.81
Creatinine, mean±SD, mg/dL	1.23±1.05	1.17±1.37	0.65
CRP, mean±SD, mg/L	94.39±84.51	85.58±77.41	0.4
D-dimer, mean±SD, mg/L	2.75±5.44	1.89±3.63	0.2
Troponin-I, mean±SD, ng/L	267.4±31.5	86.2±18	0.35
Brain natriuretic peptide, mean±SD, pg/mL	410.63±915.93	130.19±238.57	0.044
Bilateral infiltrate, n (%)	28 (45.16)	183 (45.75)	0.85
Atrial fibrillation, n (%)	8 (16.67)	14 (4.59)	0.0047
ST/T-wave changes, n (%)	11 (22.92)	49 (16.07)	0.299
Echocardiography			
LVEF, mean±SD, %	56.36±7.42	57.62±6.22	0.29
Left ventricle end-diastolic diameter, mean±SD, mm	43.15±6.77	44.27±6.73	0.2
Left ventricle end-diastolic index, mean±SD, mm/m^2	23.5±3.4	23.5±4.1	0.79
Left ventricle end-systolic diameter, mean±SD, mm	28.12±7.32	28.92±6.53	0.38
Left ventricle end-systolic index, mean±SD, mm/m^2	15.4±3.6	15.2±4.3	0.75
Left atrial volume index, mean±SD, mL/m^2	34.8±17.3	30.8±13.1	0.09
RV end-diastolic area index, mean±SD, cm^2/m^2	11.3±2.7	11.2±2.5	0.77
RV end-systolic area index, mean±SD, cm^2/m^2	6.5±1.7	6.6±2.1	0.82
RV fractional area change, mean±SD, %	41.5±13.0	42.2±11.9	0.82
TAPSE, mean±SD, cm	2.01±0.5	2.31±0.67	<0.0001

(*Continued*)

Table 1. Continued

Variables	Pericardial effusion (n=75)	Without pericardial effusion (n=455)	*P* value
RV S', mean±SD, cm/s	10.33±2.87	11.29±2.7	0.01
Stroke volume index, mean±SD, mL/m^2	31.0±9.5	32.6±9.3	0.24
Cardiac index, mean±SD, L/min per m^2	2.25±0.78	2.60±1.88	0.02
E-wave velocity, mean±SD, cm/s	72.51±24.09	65.44±19.84	0.02
A-wave velocity, mean±SD, cm/s	66.81±22.15	62.24±19	0.14
E/A ratio	1.07±0.4	1.5±8.05	0.29
e' Septal, mean±SD, cm/s	6.24±1.84	6.71±2.08	0.055
e' Lateral, mean±SD, cm/s	7.58±2.54	8.73±3.12	0.001
E/e' average ratio, mean±SD	11.6±5.73	9.57±4.54	0.006
Right atrial pressure, mean±SD, mm Hg	9.5±4	7.3±3.48	<0.0001
Pulmonic flow acceleration time, mean±SD, ms	73.33±26.47	90.13±26.58	<0.0001
Pulmonary vascular resistance index, mean±SD, dynes*s/cm^5 per m^2	309.4±148	214.0±148	<0.0001

LVEF indicates left ventricular ejection fraction; RV, right ventricle; RV S', systolic tricuspid lateral annular velocity; and TAPSE, tricuspid annular plane systolic excursion.

hemodynamic parameters, and MEWS, pericardial effusion was marginally associated with mortality (HR, 1.96 [95% CI, 0.89–4.09]; *P*=0.09), and marginally improved the model fit in nested model (*P*=0.09 for χ^2 difference test).

Focused Cardiac Ultrasound and Pericardial Effusion

We analyzed whether addition of evaluation for pericardial fluid increases the predictive ability above a simple echocardiographic assessment using only TAPSE and ejection fraction, without Doppler parameters. Although this simplified evaluation was inferior to the complete echocardiographic examination that included the Doppler hemodynamic parameters, it was still significantly associated with mortality and additive to clinical assessment and MEWS (Table 3). In multivariate analysis adjusted for TAPSE and ejection fraction, pericardial effusion was associated with mortality (HR, 2.3 [95% CI, 1.39–3.68]; *P*=0.0007), and improved the model fit in nested model (*P*=0.0001 for χ^2 difference test). In multivariate analysis adjusted for TAPSE, LVEF, and MEWS, pericardial effusion was associated with mortality (HR, 1.86 [95% CI, 1.09–3.07]; *P*=0.02), and improved the model fit in nested model (*P*=0.02 for χ^2 difference test).

DISCUSSION

This study evaluates the prevalence, associates, and clinical implication of pericardial involvement in hospitalized patients with COVID-19. Its main findings are as follows: (1) The prevalence of pericardial effusion in a cohort of hospitalized patients across all disease severity of COVID-19 infection is around 14%. (2) Pericardial effusion is associated with COVID-19 severity, worse RV systolic function, and elevated BNP, but rarely with acute pericarditis or myocardial injury. (3) Pericardial effusion is associated with excess mortality. (4) Combining assessment for pericardial effusion with a simple focused echocardiographic evaluation (LVEF and TAPSE) is a strong predictor of outcome in hospitalized patients with COVID-19 infection.

Prevalence and Associates of Pericardial Effusion

The association of pericardial disease with infections was first reported in 1933.[29] Since then, it was described in various viral infections, with Enteroviruses, Coxsackie, and Herpesviruses being the most common.[23,30] The data on pericardial disease in other coronaviruses are scarce and based only on case reports.[10,31] Our data show that in consecutive hospitalized patients with COVID-19 infection, the prevalence of pericardial effusion was nearly 15%, but only 17 of 530 (3.2%) had pericarditis. Several recent small prospective studies in critically ill patients with COVID-19[11–13] have described a prevalence ranging from 43% to 90% for pericardial effusion. Other publications have dealt with the prevalence and clinical impact of pericardial effusion in acute COVID-19 infection.[6,8–10] However, all these reports were either retrospective or based on systematic literature review, assessing only patients with clinically indicated echocardiographic examinations. Our study used a prospectively defined protocol and included unselected hospitalized patients encompassing all grades of disease severity, which can better evaluate the prevalence and clinical impact of pericardial effusion in hospitalized patients with COVID-19. Recently, Brito

Table 2. OR for Association of Pericardial Effusion and Clinical, Laboratory, and Echocardiographic Parameters

Parameter	Univariate analysis OR	Multivariate analysis OR
Clinical and laboratory		
Age	1.02 (1.01–1.04)*	
MEWS	1.13 (1.05–1.21)*	1.16 (1.03–1.32)*
Hemoglobin	0.82 (0.73–0.93)*	
BUN	1.01 (1.002–1.02)†	
Creatinine	1.03 (0.88–1.22)	
BNP	1.001 (1.0003–1.002)*	1.001 (1.004–1.002)*
Troponin-I	1.000 (0.99–1.004)	
CRP	1.001 (0.99–1.004)	
Ischemic heart disease	2.33 (1.32–4.1)*	
Atrial fibrillation	2.04 (1.06–3.9)†	
Left ventricle		
LVEF	0.97 (0.94–1.02)	
Stroke volume index	0.98 (0.95–1.01)	
Cardiac index	0.63 (0.42–0.95)†	
E/e'	1.07 (1.03–1.12)*	
Right ventricle		
TAPSE	0.31 (0.18–0.53)*	0.47 (0.21–0.97)†
RV S'	0.86 (0.78–0.96)*	
RA pressure	1.15 (1.08–1.22)*	
Pulmonic acceleration time	0.97 (0.96–0.98)*	
Calculated PVR index	1.005 (1.003–1.007)*	
χ^2 Value for multivariate model		31.8
P value for multivariate model		<0.0001
AUC for multivariate model		0.77

AUC indicates area under the curve; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; MEWS, modified early warning score; OR, odds ratio; PVR, pulmonary vascular resistance; RA, right atrial; RV S', systolic tricuspid lateral annular velocity; and TAPSE, tricuspid annular plane systolic excursion.

*$P<0.005$.

†$P<0.05$.

et al[32] studied the presence of pericardial inflammation in a small cohort of 54 athletes recovering from COVID-19 infection. Although 39.5% had pericardial late enhancement on cardiac magnetic resonance imaging, only 6% had associated pericardial effusion by echocardiography. The possible reasons for the lower prevalence of pericardial effusion compared with the present cohort are the younger age of patients, milder disease (all athletes were not hospitalized, and had either mild or asymptomatic disease), and performing the echocardiography at a later stage (around 28 days after COVID-19 diagnosis).

A large retrospective trial reported a pericarditis prevalence of 1.5% in patients with COVID-19 in the United States based on *International Classification of Diseases, Tenth Revision* (*ICD-10*), diagnosis codes.[20] The use of retrospective data and diagnosis codes, in contrast to the present study, may contribute to underestimation of the prevalence of pericarditis in patients with COVID-19.

Surprisingly, the prevalence of pericarditis in patients with pericardial effusion was low, and neither CRP nor troponin-I levels were associated with pericardial effusion. The data suggest that pericardial or myocardial inflammation does not play a major role in the cause of pericardial effusion in patients with COVID-19 infection.

Outcome

Hospitalized patients with COVID-19 infection and pericardial effusion had a worse outcome compared with patients without pericardial effusion in nonadjusted analysis. There are several possible mechanisms for pericardial involvement in patients with COVID-19. These include direct viral injury to the myocardium, extending to the pericardium; activation of exaggerated inflammatory response to the viral infection with secondary myocardial and pericardial involvement; acute respiratory distress syndrome, resulting in cardiac hypoxic injury extending to the pericardium; or hypoxia causing pulmonary hypertension, leading to pericardial effusion.[8,10] Mechanisms related to secondary injury are implied by our data, showing pericardial effusion in patients with COVID-19 infection is strongly associated with worse pulmonary disease and RV dysfunction, as well as with elevated BNP. Thus, we believe that a pericardial effusion is usually a surrogate marker of more severe COVID-19 infection. More important, although several case reports have shown that pericardial effusions may deteriorate to tamponade,[16,18] causing direct hemodynamic compromise and death, this is extremely rare, and was not the mechanism of mortality in any one of the patients. In multivariate analysis adjusted for clinical, echocardiographic, and hemodynamic parameters, pericardial effusion was marginally associated with mortality in hospitalized patients. In a previous work, we were able to show that noninvasive echocardiographic hemodynamic parameters, such as low forward flow, high left and right filling pressures, and high RV afterload, are strongly associated with mortality.[33,34] This emphasized the importance of obtaining Doppler-based hemodynamic parameters in patients with severe COVID-19 infection. However, at the same time, we showed that in patients with mild disease, or low MEWS, mortality is low, irrespective of hemodynamic parameters. Thus, to decrease the risk of exposure, we recommended complete hemodynamic evaluation only when clinically indicated, or

LOW RESOLUTION COLOR FIG

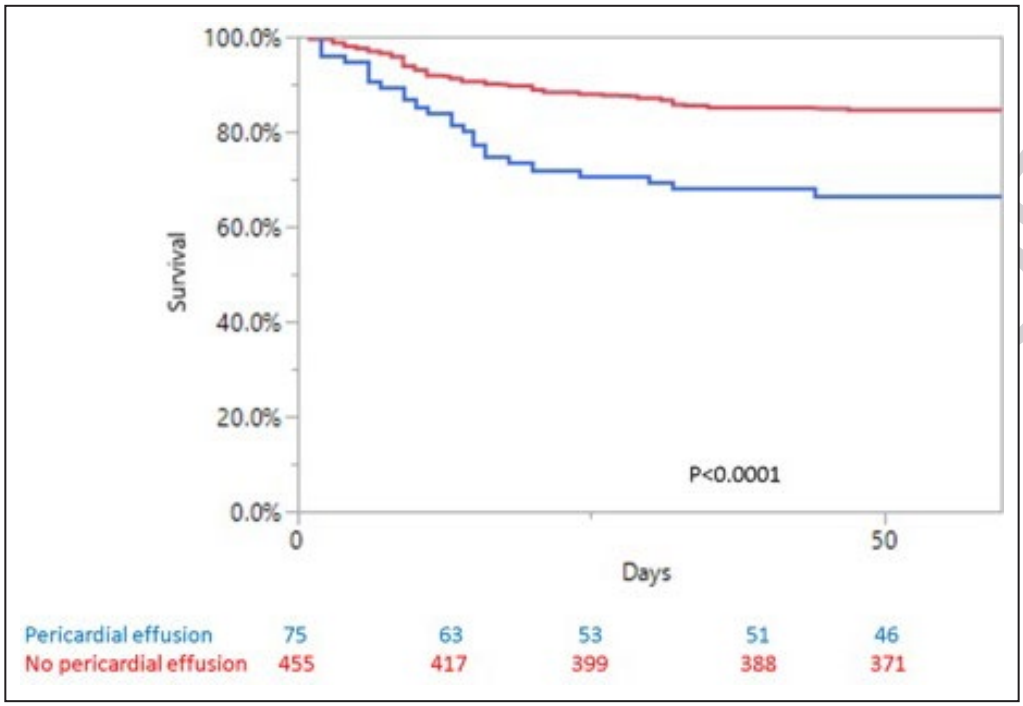

Figure 2. Outcome of patients with COVID-19 infection, stratified according to presence or absence of pericardial effusion.
Overall survival in patients with COVID-19 infection, comparing patients with pericardial effusion (blue line) and no pericardial effusion (red line).

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in patients with high MEWS. In the present work, we demonstrate that once comprehensive noninvasive hemodynamic evaluation is performed, pericardial effusion has only marginal additive value for predicting mortality. However, once limited echocardiography is performed, simple evaluation for the presence of pericardial effusion has significant additive predictive value in hospitalized patients.

Focused Cardiac Ultrasound and Clinical Implications

Recent documents published by the European Association of Cardiovascular Imaging and the American Society of Echocardiography recommended a focused cardiac ultrasound approach in patients with COVID-19.[24,35] In a previous work,[33] we found that a limited echocardiographic evaluation, including only TAPSE and LVEF, provides valuable information for clinical management. Recent advances in ultrasound technology have led to the miniaturization of machines to the size of a mobile telephone, which do not provide spectral Doppler functions.[36] We show that in the context of hospitalized patients with COVID-19, assessment for presence of pericardial effusion, combined with LVEF and TAPSE from the 4-chamber view alone, carries significant prognostic data, on top of clinical evaluation and risk scores. This may further help risk stratify patients with COVID-19 in a reality of overwhelmed health systems.

Study Limitations

This single-center study included only hospitalized patients with COVID-19. The fact that only a minority of patients with COVID-19 are admitted to the hospital may lead to overestimation of the prevalence and clinical impact of pericardial effusion in COVID-19. Furthermore, the presence of preexisting pericardial effusion cannot be excluded, resulting in possible overestimation of the true incidence of pericardial effusion. Eighty patients were excluded because they had "do not resuscitate/intubate" orders and thus received palliative care and died shortly after admission without echocardiographic assessment. This may create an opposite bias, resulting in underestimation of the prevalence and impact of pericardial effusion in patients with COVID-19. Pre–COVID-19 echocardiograms were not evaluated, and some of the findings may have preceded COVID-19 infection. Echocardiography was performed by cardiologists with expertise in echocardiography using a mobile system and not a pocket-size handheld device. Thus, our hypothesis about the use of handheld devices for limited examinations should serve as an incentive to explore this concept in dedicated prospective series.

Table 3. HR for Association of Pericardial Effusion With Mortality

Variable	Univariate analysis HR	Multivariate analysis HR
Mortality with echocardiographic findings		
Pericardial effusion	2.44 (1.50–3.83); *P*=0.0005	1.83 (0.95–3.4); *P*=0.06
Ejection fraction	0.95 (0.93–0.98); *P*=0.0008	1.02 (0.98–1.07); *P*=0.26
Stroke volume index	0.95 (0.91–0.98); *P*=0.001	0.95 (0.91–0.99); *P*=0.01
E/e' average	1.09 (1.06–1.11); *P*<0.0001	1.06 (1.02–1.10); *P*=0.003
Pulmonic AT	0.97 (0.96–0.98); *P*<0.0001	0.98 (0.96–0.99); *P*=0.003
TAPSE	0.4 (0.27–0.63); *P*<0.0001	1.10 (0.57–1.64); *P*=0.74
χ^2 Value for model		46.7
P value for model		<0.0001
AIC		534
χ^2 Value for model without pericardial effusion		42.9
P value for χ^2 difference test for nested model		0.05
Mortality with echocardiographic findings and MEWS		
Pericardial effusion	2.44 (1.50–3.83); *P*=0.0005	1.86 (0.95–3.5); *P*=0.06
Ejection fraction	0.95 (0.93–0.98); *P*=0.0008	1.04 (0.98–1.09); *P*=0.1
Stroke volume index	0.95 (0.91–0.98); *P*=0.001	0.96 (0.93–0.99); *P*=0.04
E/e' average	1.09 (1.06–1.11); *P*<0.0001	1.08 (1.03–1.12); *P*=0.0006
Pulmonic AT	0.97 (0.96–0.98); *P*<0.0001	0.99 (0.97–1.00); *P*=0.45
TAPSE	0.4 (0.27–0.63); *P*<0.0001	1.10 (0.71–1.43); *P*=0.55
MEWS	1.4 (1.32–1.51); *P*<0.0001	1.47 (1.33–1.64); *P*<0.0001
χ^2 Value for model		102.6
P value for model		<0.0001
AIC		452.9
χ^2 Value for model without pericardial effusion		99.1
P value for χ^2 difference test for nested model		0.07
Mortality with echocardiographic findings, MEWS, and other clinical parameters		
Pericardial effusion	2.44 (1.50–3.83); *P*=0.0005	1.96 (0.89–4.09); *P*=0.09
Ejection fraction	0.95 (0.93–0.98); *P*=0.0008	1.02 (0.98–1.09); *P*=0.24
Stroke volume index	0.95 (0.91–0.98); *P*=0.001	0.96 (0.92–1.01); *P*=0.13
E/e' average	1.09 (1.06–1.11); *P*<0.0001	0.97 (0.90–1.09); *P*=0.25
Pulmonic AT	0.97 (0.96–0.98); *P*<0.0001	1.001 (0.98–1.02); *P*=0.87
TAPSE	0.4 (0.27–0.63); *P*<0.0001	0.59 (0.25–1.36); *P*=0.22
MEWS	1.4 (1.32–1.51); *P*<0.0001	1.27 (1.13–1.43); *P*<0.0001
Troponin	4.1 (2.7–6.2); *P*<0.0001	1.000 (0.99–1.00001); *P*=0.17
BNP	4.9 (3.0–8.3); *P*<0.0001	1.0001 (1.006–1.009); *P*=0.04
Age	1.07 (1.06–1.09); *P*<0.0001	1.06 (1.02–1.10); *P*=0.002
χ^2 Value for model		77.2
P value for model		<0.0001
AIC		326.1
χ^2 Value for model without pericardial effusion		74.4
P value for χ^2 difference test for nested model		0.09
Mortality with focused echocardiography		
Pericardial effusion	2.44 (1.50–3.83); *P*=0.0005	2.3 (1.39–3.68); *P*=0.0007
Ejection fraction	0.95 (0.93–0.98); *P*=0.0008	0.97 (0.94–1.00); *P*=0.05
TAPSE	0.4 (0.27–0.63); *P*<0.0001	0.55 (0.34–0.88); *P*=0.01
χ^2 Value for model		29.7

(*Continued*)

Table 3. Continued

Variable	Univariate analysis HR	Multivariate analysis HR
P value for model		<0.0001
AIC		1020.5
χ^2 Value for model without pericardial effusion		19.6
P value for χ^2 difference test for nested model		0.0001
Mortality with focused echocardiography and MEWS		
Pericardial effusion	2.44 (1.50–3.83); *P*=0.0005	1.86 (1.09–3.07); *P*=0.02
Ejection fraction	0.95 (0.93–0.98); *P*=0.0008	0.97 (0.95–1.00); *P*=0.05
TAPSE	0.4 (0.27–0.63); *P*<0.0001	0.88 (0.59–1.13); *P*=0.41
MEWS	1.4 (1.32–1.51); *P*<0.0001	1.39 (1.29–1.49); *P*<0.0001
χ^2 Value for model		118.7
P value for model		<0.0001
AIC		797.6
χ^2 Value for model without pericardial effusion		113.0
P value for χ^2 difference test for nested model		0.02

AIC indicates Akaike information criterion; AT, acceleration time; BNP, brain natriuretic peptide; HR, hazard ratio; MEWS, modified early warning score; and TAPSE, tricuspid annular plane systolic excursion.

CONCLUSIONS

In a large prospective cohort of consecutive hospitalized patients with COVID-19 infection encompassing the entire spectrum of disease severity, pericardial effusion is common, but rarely is attributable to acute pericarditis or myocarditis. Nevertheless, it is associated with myocardial dysfunction and excess mortality. To achieve significant clinical value for risk stratification, a limited echocardiographic examination, including LVEF, TAPSE, and evaluation for presence of pericardial effusion, is sufficient.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S2

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