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COVID-19-related echocardiographic patterns of cardiovascular dysfunction in critically ill patients: A systematic review of the current literature

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ABSTRACT

Purpose: Coronavirus disease 2019 (COVID-19) infection may trigger a multi-systemic disease involving different organs. There has been growing interest regarding the harmful effects of COVID-19 on the cardiovascular system. This systematic review aims to systematically analyze papers reporting echocardiographic findings in hospitalized COVID-19 subjects.

Materials and methods: We included prospective and retrospective studies reporting echocardiography data in >10 hospitalized adult subjects with COVID-19; from 1st February 2020 to 15th January 2021.

Results: The primary electronic search identified 1120 articles. Twenty-nine studies were finally included, enrolling 3944 subjects. Overall the studies included a median of 68.0% (45.5–100.0) of patients admitted to ICU. Ten studies (34.4%) were retrospective, and 20 (68.9%) single-centred. Overall enrolling 1367 subjects, three studies reported normal echocardiographic findings in 49 ± 18% of cases. Seven studies (24.1%) analyzed the association between echocardiographic findings and mortality, mostly related to right ventricular (RV) dysfunction.

Conclusions: Data regarding the use of echocardiography on hospitalized, predominantly ICU, COVID-19 patients were retrieved from studies with heterogeneous designs, variable sample sizes, and severity scores. Normal echocardiographic findings were reported in about 50% of subjects, with LVEF usually not affected. Overall, RV dysfunction seems more likely associated with increased mortality.

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1. Introduction

At the end of January 2021, less than one year after its recognition as a pandemic outbreak by the World Health Organization, the coronavirus

disease 2019 (COVID-19) has counted more than 100 million cases in 192 countries leading to over 2,000,000 deaths [1]. The main feature of severe COVID-19 is the development of interstitial pneumonia with highly variable clinical characteristics, ranging from asymptomatic or mild and self-limiting cases to severe disease with the acute respiratory syndrome (SARS-CoV-2) requiring intensive care unit (ICU) admission and mechanical ventilation [2–4].

Despite its prevalent lung tropism associated with prominent functional and morphological features [5], it is now clear that COVID-19 infection may trigger a multi-systemic disease involving different organs [6–9]. There is growing evidence regarding the harmful effects of COVID-19 on the cardiovascular system with acute events, such as

Abbreviations: ICU, intensive care unit; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe disease with the acute respiratory syndrome; LV, left ventricle; RV, right ventricle; EF, ejection fraction; TAPSE, Tricuspid Annular Plane Systolic Excursion; GLS, global longitudinal strain.

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myocardial infarction during the initial phase and long-term consequences after clinical recovery. A recent study conducted on young professional athletes recovering after COVID-19 without the need for hospitalization showed that a non-negligible number (15%) had evidence of myocarditis on cardiac magnetic resonance [10–13].

There are several possible patterns of cardiovascular dysfunction associated with COVID-19: signs of direct inflammatory (myocarditis) or ischemic (infarction) insult, hypovolemia (due to sustained fever and dehydration), right ventricular (RV) dysfunction related to the effects of mechanical ventilation and/or pulmonary embolism, or, eventually, cardiovascular dysfunction due to super-imposed bacterial or fungal sepsis [5,10,11,13,14]. Accordingly, the echocardiographic findings in COVID-19 hospitalized subjects may also be variable. They range from specific regional wall motion abnormalities of the left ventricle (LV) or RV to different degrees of global cardiac dysfunction related to myocarditis or a systemic deregulated inflammatory response to viral infection [15–18]. Echocardiography thus may have a crucial role in distinguishing these patterns, guiding therapeutic approaches, and tracking the clinical response over time.

We conducted a systematic review to summarise the current knowledge regarding cardiac dysfunction in COVID-19 as assessed by echocardiography, both in ICU and non-ICU subjects.

2. Materials and methods

We adhered to the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis - Protocols* (PRISMA-P) guidelines [19] (Supplemental Table S1 in the Supplemental Materials). This study's protocol was registered with the *International Prospective Register of Systematic Reviews* (PROSPERO) in November 2020 (CRD42020218439).

2.1. Eligibility criteria, identification and selection of the studies, and data extraction

A systematic literature search was performed, including the following databases: MEDLINE®, EMBASE® and the Cochrane Database of Systematic Reviews. The systematic search was performed combining the terms: 'heart function' OR 'heart failure' OR 'cardiac' OR 'disease' AND 'coronavirus disease 2019', with filters for adult patients (Supplemental Table S2 in the Supplemental Materials), up to 15th January 2021.

We included prospective and retrospective studies reporting echocardiography data in hospitalized adult subjects with COVID-19 regardless of disease severity and the ward where the echocardiographic examination was performed. We excluded editorials and letters to the editor, reviews, studies conducted in the pediatric population, or those enrolling less than 10 participants. We applied language restrictions and excluded articles not written in English, Spanish, French or Italian.

Inclusion criteria for clinical studies were pre-specified according to the PICOS approach:

- P: patients with COVID-19 disease;
- I: received an echocardiographic examination during hospitalization;
- C: regardless of the presence of comparison between subgroups;
- O: data provided according to disease severity, hospitalization site, myocardial injury, and/or survival.

S: prospective or retrospective studies and case series with at least 10 subjects.

Two examiners (L.C. and An.Mi.) independently evaluated titles and abstracts. The articles were then subdivided into three subgroups: "included" and "excluded" (if the two examiners agreed with the selection) or "uncertain" (in case of disagreement). In the case of "uncertain" classification, discrepancies were resolved by further examination performed by two expert authors (A.M. and F.S.). Full-text articles identified as potentially relevant were evaluated with PICOS criteria. We used a standardized electronic spreadsheet (Microsoft

Excel, V14.4.1; Microsoft, Redmond, WA) to extract data from all included studies (Supplemental Table S3 in the Supplemental Materials). We recorded: trial characteristics (*i.e.*, number of centers, country), subject population (*i.e.*, demographics, baseline illness severity scores, ward/ICU admission), echocardiographic findings, and clinical outcomes (*i.e.*, mortality, morbidity related to organ-specific function or infections). When necessary, the included studies' corresponding authors were contacted to obtain missing data.

2.2. Echocardiographic measurements of interest

We *a priori* planned to divide the echocardiographic findings reported by the included studies according to predefined three main domains:

- 1) LV systolic function [*i.e.*, LV ejection fraction (LVEF)] and myocardial performance (global longitudinal strain - GLS);
- 2) LV diastolic function;
- 3) RV function [*i.e.*, Tricuspid Annular Plane Systolic Excursion (TAPSE)].

2.3. Statistical analysis

Statistical analysis was conducted on the summary statistics described in the selected articles (*e.g.*, means, medians, proportions) and, therefore, the statistical unit of observation for all the selected variables was the single study and not the single subject.

Descriptive statistics of individual studies used different statistical indicators for central tendency and variability, such as means and standard deviations (*i.e.*, demographic data, echocardiographic measurements, and severity scores), whereas absolute and relative frequencies were adopted for qualitative variables. To show one single indicator for the quantitative variables, we collected means with standard deviations (SD) or medians and inter-quartile ranges (IQR), as appropriate.

3. Results

As shown in Fig. 1, the primary electronic search identified 1120 articles. The examiners identified 41 potentially relevant studies from the title and abstract analysis, but 12 studies were judiciously excluded. The PRISMA flowchart of study selection is shown in Fig. 1. The list of the excluded studies is also reported in Supplemental Table S4 in the Supplemental Materials.

We finally included 30 studies in the analysis, including 4012 subjects overall. Table 1 describes the baseline characteristics of the included studies [68% (10) males], with a median age of 64 (4) years and Body Mass Index of 28 (26–29) Kg/m². Hypertension was the most commonly reported comorbidity [54 (15)]. Overall, the studies included a median of 52.0% (0.0–100.0) of patients admitted to ICU, undergoing forms of invasive or non-invasive mechanical ventilation in 57.0% (34.0–81.0) and 13.0% (8.6–32.7) of cases, respectively. Ten studies (32.2%) were retrospective [17,20–28], and 20 (66.6%) monocentric [15,17,18,20–22,24–38].

Echocardiographic findings are shown in Table 2 (LV systolic function and GLS values), Table 3 (LV diastolic parameters), and Table 4 (RV function). Studies are listed in an order that follows the presence of homogeneous criteria for subgroup analysis (*i.e.*, study population divided according to myocardial injury, or survival, or ICU admission, *etc.*). Studies with no subgroup analyses are reported at the bottom of each table.

3.1. General considerations

Three studies [34,35,39] enrolling a total of 1367 subjects reported a mean of 49% ± 18 normal echocardiographic findings. Kim et al. (n = 510 patients) reported a normal LVEF in 304 (59.6%) subjects, regional LV wall motion abnormality in 63 (12.3%) and RV dysfunction in 41

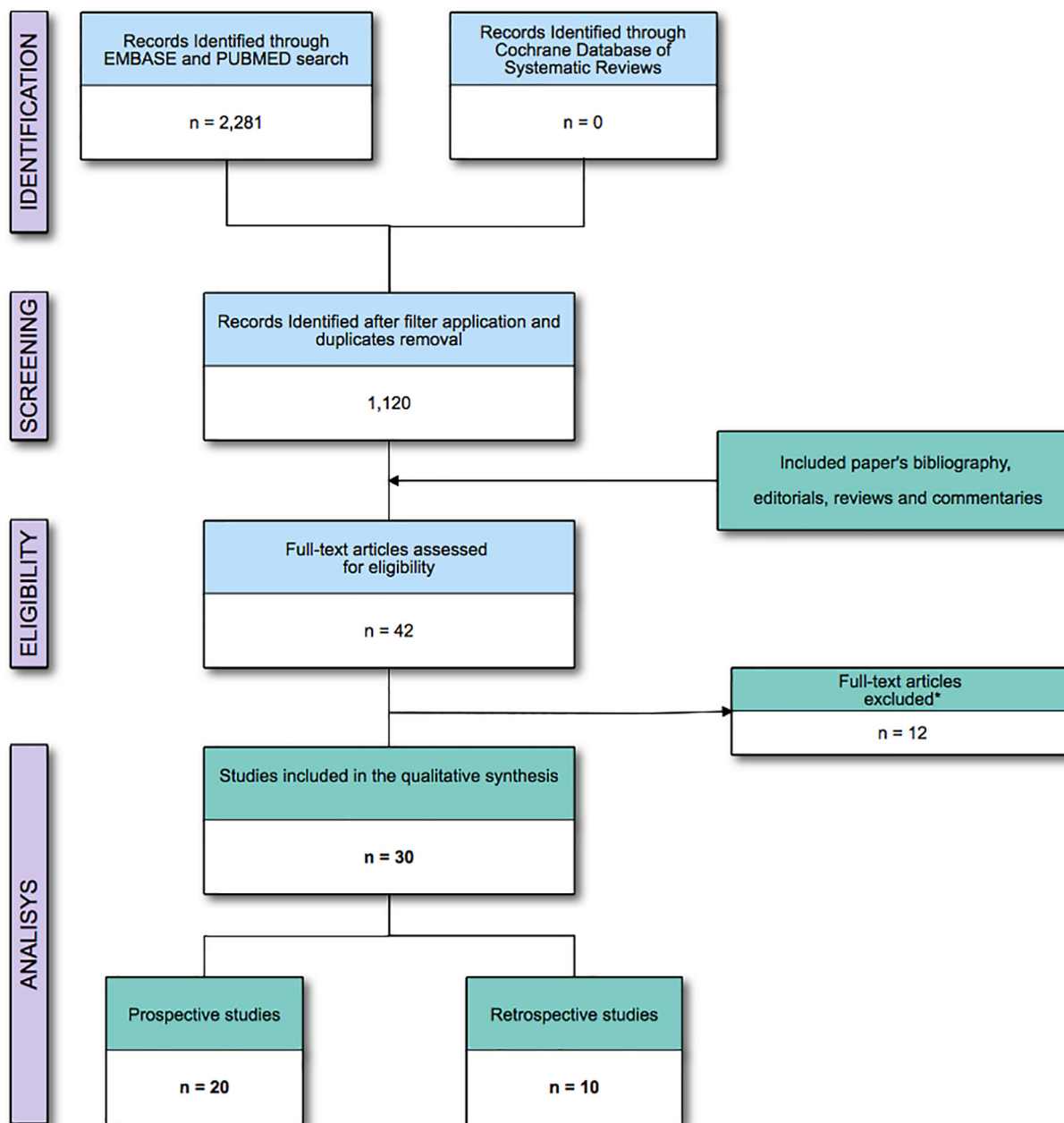


Fig. 1. Flow of the studies. * = Not fitting eligibility criteria full text articles excluded a reported in the Supplemental Table S4 in the Supplemental Materials.

(8.0%) [40]. Giustino et al. (n = 305) reported a normal LVEF in 228 (74.8%) subjects, normal/grade I diastolic dysfunction in 167 (54.7%) and normal RV function in 236 (79.2%) [41].

3.2. LV systolic function and strain

Few studies reported an impaired LVEF. Two studies reported a mean LVEF of 49% in non-survivors compared to a normal LVEF in survivors [24,32]. Rodriguez-Santamaria et al. reported an impaired LVEF in 6 of 37 non-ICU patients (16%) [36], while Kim et al. reported a mean LVEF of 45.2% in 41 of 510 patients (8.0%) having a concomitant RV dysfunction.

Seven studies (24.1%) [16,18,24,29–31,35] reported an advanced assessment of either LV GLS. Among the 49 subjects included in the study of Bursi et al., non-survivors (33%) showed a significantly lower LV GLS [24]. Lairez et al. reported no difference in the LV GLS among subjects

having (n = 13) or not having (n = 18) a concomitant troponin raise. [31] Van der Heuvel et al. reported an abnormal LV GLS in 11 of 51 (21.5%) of non-ICU subjects [35]. Stöbe et al. reported abnormal LV deformation, especially in basal segments, in 14 subjects with normal LVEF [18]. This finding is consistent with Goerlich et al. reporting a reduced basal strain in 39/75 subjects (52%), having a lower GLS than those with normal basal strain [30].

The cardiac output measurements employing echocardiography have been evaluated only in 4 studies, reporting overall normal values, but the included populations were not homogeneous [29,34,40,42] (Supplemental Table S5 in the Supplementary Materials).

3.3. LV diastolic function

We found no studies reporting a complete LV diastolic assessment according to the most recent guidelines [43], thus including E and e'

Table 1
General characteristics of the study populations.

Authors	Patients (n)	Age (years)	Male (%)	B.M.I.	Time to echo (days)	HTN (%)	DM (%)	Obesity (%)	CAD (%)	Stroke (%)	CKD (%)	COPD (%)	IMV (%)	NIV (%)	ICU (%)
Garcia-Cruz et al. [42]	82	56 (50–66)	62.2	–	0 (0)	47.6	43.9	–	–	–	–	–	79	21	100
Van den Heuvel et al. [35]	51	63 (51–68)	80	27 (25–29)	–	41	18	–	10	4	2	12	33	–	37
Rath et al. [32]	123	68 (15)	62.2	28 (5)	–	69.9	24.4	19.5	22.8	–	11.4	–	40	–	45.5
Chen et al. [25]	143	67 (16)	62	29 (6.3)	–	69	38	–	30	10	19	–	35	–	–
Schott et al. [45]	66	60 (16)	57.6	43 (12)	3 (4.5)	57.6	34.8	–	15.2	–	4.5	12.1	34.8	–	57.6
Jain et al. [28]	72	–	72.2	–	–	66.7	43.1	47.2	18.1	–	22.2	20.8	55.6	–	–
Dweck et al. [39]	1216	62 (52–71)	70	–	–	37	19	–	14	–	–	–	–	–	60
Giustino et al. [41]	305	63 (53–73)	67.2	28 (24–33)	4 (1–10)	59.3	37.4	–	7.4	9.5	19.3	5.9	34.5	–	–
Bursi et al. [24]	49	66 (13)	63.3	–	8 (4–15)	49	18.4	–	22.4	10.2	–	12.2	22	36.7	–
Stobe et al. [18]	18	64 (19)	78	–	–	72	28	–	11	17	39	5	22.2	11.1	–
Szekely et al. [34]	100	66 (17)	63	–	0 (0)	57	29	29	16	11	10	4	–	–	–
Mahmoud-Elsayed et al. [17]	74	59 (13)	78	–	5 (3–10)	42	36	–	9	7	11	–	78	–	–
Labbè et al. [22]	92	62 (53–69)	78.3	28 (24–31)	0 (0)	63	26.1	–	17.4	–	–	–	90.2	9.8	100
Doyen et al. [44]	43	60 (13)	84	29 (5)	–	33	28	–	5	–	14	–	95	5	100
Stockenhuber et al. [33]	34	72 (3)	79	–	–	53	35	–	–	–	32	–	37	–	–
Deng et al. [21]	112	65 (49–71)	50.9	–	–	32.1	17	–	13.4	–	–	–	25	–	23.2
Baycan et al. [29]	100	54 (15)	58	23 (3)	–	26	14	–	–	–	–	–	–	35	22
Li et al. [20]	49	64 (13)	54.3	–	–	34.3	22.9	–	–	–	–	–	13	–	18.9
Kim et al. [40]	510	64 (14)	66	–	–	63	41	34	–	–	–	6	60	–	68
Rodríguez-Santamarta et al. [36]	37	68 (60–71)	91.9	–	–	–	–	–	5.4	–	2.7	21.6	–	–	100
Goerlich et al. [30]	75	62 (13)	59	29 (26–34)	4	68	32	–	9	–	–	–	61	12	73
Moody et al. [23]	164	61 (13)	78	31 (6)	–	41	32	–	13	–	–	12	73	–	–
Goerlich et al. [27]	73	66 (57–75)	55	29 (26–35)	4 (2–7)	67.1	42.5	–	19.2	–	–	13.7	–	–	75.3
Zeng et al. [26]	35	64 (59–68)	66	24.6 (3.3)	–	37	29	–	6	–	0	3	100	0	100
Lariez et al. [31]	16	62 (16)	63	25.2 (3.3)	0 (0)	50	13	13	–	–	0	13	68	–	68
Barman et al. [15]	44	63.3 (16)	54	30.1 (5.6)	–	52	22	–	0	0	0	0	54	–	65
Lassen et al. [16]	214	68.6 (13)	54.7	27.2 (4.8)	4 (2–8)	57	8.4	–	11.2	–	–	6.5	–	–	–
Lazzeri et al. [37]	28	61.7 (10)	79	28.4 (5)	0 (0)	89	39	–	28.6	–	3.5	7	86	14	100
D'alto et al. [64]	69	62 (13)	77	–	–	64	16	26	20	–	–	–	17	32	100
Evrard et al. [38]	18	70 (57–75)	67	29 (26–32)	–	61	22	–	–	–	–	–	100	0	100

As reported in the papers, data are shown as mean (standard deviation) or median (25th – 75th Interquartile). BMI, body mass index; DM, Diabetes mellitus; CAD, Coronary artery occlusive disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HTN: hypertension; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; ICU, intensive care unit.

wave velocities, E/A and E/e' ratio, left atrium size, and tricuspid regurgitant jet velocity. Lariez et al., in a small population of 31 subjects, reported that the lateral mitral annular diastolic velocity was significantly lower in those subjects presenting an increase in plasmatic troponin levels compared to others (10 ± 3 vs. 13 ± 3 , $p = 0.03$) [31]. Stöbe et al. reported a higher E/e' ratio ($p < 0.005$) in 14 subjects requiring mechanical ventilation compared to 4 with less severe disease [18]. However, this finding was not confirmed in two more extensive studies stratifying subjects according to the severity of COVID-19 infection [29,34]. Garcia-Cruz et al. reported a significant progressive increase of both the E/A ($p = 0.001$) and E/e' ($p = 0.03$) ratios from subjects with normal oxygenation to those with severe ARDS [42].

3.4. RV systolic function

Only one study reported a slightly reduced mean TAPSE of 15.3 mm in non-survivors than survivors [33]. Doyen et al. reported that TAPSE, within the normality range, was lower in subjects with increased plasmatic troponin levels than others (19 ± 5 vs. 23 ± 3 , $p = 0.01$) [44]. RV function assessment has been performed using quantitative/semi-quantitative [28,32,41] (i.e., adopting either the TAPSE or RV fractional area change) or a qualitative operator-dependent evaluation [25,45].

Both Lassen et al. and Baycan et al. showed a significant difference in RV longitudinal strain and GLS. in COVID-19 subjects compared to controls [16,29]. Moreover, Bursi et al. found significantly lower RV GLS and free wall strain in non-survivors [24]. The criteria for RV dysfunction are reported in Supplemental Table S6 in the Supplementary Materials.

3.5. Clinical outcomes

Seven studies (24.1%) reported a logistic regression model analysis showing an association between echocardiographic findings and mortality [16,23,24,32–34,40].

Low LVEF was associated with increased mortality [univariable model: OR = 3.2 OR (95%CI 1.01–8.1); $p = 0.04$ for 10% difference] [34]; multivariable model: OR = 12.19 (95%CI 2.87–51.83); $p = 0.001$ [32]].

Considering RV function, reduced TAPSE [univariable model: HR = 1.23 (95%CI 1.11–1.36), $p < 0.001$ [16]; simple comparison ($p = 0.049$) [33]], RV dilation/dysfunction [multivariable model: HR = 2.70 (95%CI 1.68–4.36), $p < 0.001$ [40]], and RV systolic dysfunction [multivariable model: HR = 1.80 (95%CI 1.05–3.09); $p = 0.032$ [23]] were all different in non-survivors as compared to survivors. Considering the strain assessment in a multivariable model, Baycan et al. reported

Table 2
Left ventricular (LV) systolic function and strain.

Authors and subgroup of patients	LVEF (%)		LV-EDD (mm)		LV-ESD (mm)		LV-GLS (%)	
Giustino et al. [41]	60.0 (47.5–65.0)		45 (40–50)		31 (27–38)		–	
Myocardial injury yes vs no	58.0 (42.0–65.0)	61.0 (58.0–65.0)	46 (41–51)	44 (40–49)	32 (27–40)	30 (28–36)	–	
Lariez et al. [31]	–		–		–		–	
Myocardial injury yes vs no	66 ± 8	68 ± 6	–		–		–18 ± 3	–19 ± 3
Labbe et al. [22]	60 (50–60)		–		–		–	
Myocardial injury yes vs no	55 (50–60)	60 (55–60)	–		–		–	
Doyen et al. [44]	64 ± 10		–		–		–	
Myocardial injury yes vs no	62 ± 10	68 ± 7	–		–		–	
Van den Heuvel et al. [35]	59 (54.5–60.0)		48 (45–54)		34 (30–37)		–18.5 (–19.7 – –16.9)	
ICU admission yes vs no	59.0 (55.5–60.0)	58.5 (54–60.0)	–	–	–	–	–19.7 (–21.0 – –17.7 (–18.2 – –19.1)	–16.4)
Zeng et al. [26]	–		–		–		–	
ICU admission yes vs no	63.0 (59.0–66.0)	63.5 (60.0–67.0)	46.3 ± 4.6	45.8 ± 4.4	–		–	
Rath et al [32]	57 ± 8		–		–		–	
Non-survivors vs survivors	49 ± 12	58 ± 6	–		–		–	
Bursi et al. [24]	53 ± 12		–		–		–15 ± 4	
Non-survivors vs survivors	49 ± 9	55 ± 12	–		–		–16 ± 4	–12 ± 4
D'alto et al. [64]	–		–		–		–	
Non survivors vs survivors	58 ± 8	60 ± 7	49 ± 4	48 ± 5	31 ± 5	29 ± 7	–	
Stockenhuber et al. [33]	61.0 ± 2.3		–		–		–	
Non survivors vs survivors	59.1 ± 4.0	62.5 ± 2.6	–		–		–	
Stobe et al. [18]	62.0 ± 6.5		–		–		–18.5 ± 3.7	
Mild vs severe disease	58.0 ± 4.9	63.0 ± 6.7	–		–		–19.3 ± 4.5	–18.2 ± 3.7
Barman et al. [15]	–		–		–		–	
Mild vs severe disease	61.9 ± 4.8	54.0 ± 9.8	44.9 ± 3.8	47.3 ± 5.8	28.8 ± 4.1	33.1 ± 6.7	–	
Deng et al. [21]	60.0 ± 5.6		–		–		–	
Mild vs severe disease	62.0 ± 5.5	58.5 ± 5.4	–		–		–	
Baycan et al. [29]	–		–		–		–	
Mild vs severe disease	59.9 ± 4.9	58.1 ± 4.6	46.2 ± 4.1	45.8 ± 4.9	30 ± 3.5	30.6 ± 4.9	–16.7 ± 1.3	–14.5 ± 1.8
Li et al. [20]	–		–		–		–	
Severe vs critically severe	63.9 ± 5.0	59.4 ± 8.4	45.6 ± 2.9	44.3 ± 3.0	–		–	
Szekely et al. [34]	–		–		–		–	
Mild vs moderate vs severe disease	58.2 ± 4.0	58.2 ± 5.0	56.0 ± 5.0	42.3 ± 6.0	45.1 ± 7.0	41.7 ± 4.0	26.8 ± 5.0	29.2 ± 6.0
Mahmoud-Elsayed et al. [17]	–		42 ± 8		–		–	
RV function normal vs impaired	–		42 ± 7		40 ± 10		–	
Kim et al. [40]	54.1 ± 14.4		–		–		–	
RV function normal vs impaired	45.2 ± 17.1	55.9 ± 13.5	–		–		–	
Garcia-Cruz et al. [42]	56 (53–63)		–		–		–	
P/F > 300; 201–300; 101–200; ≤100	55	54	60	62	–		–	
Lassen et al. [16]	–		–		–		–	
Control vs Cases	59.0 ± 7.2	57.6 ± 9.0	–		–		–18.5 ± 3.0	–16.4 ± 4.3
Rodriguez-Santamarta et al. [36]	55.9 ± 8.9		–		–		–	
LVEF < 50% vs ≥ 50%	40.8 ± 3.8	58.9 ± 6.2	–		–		–	
Goerlich et al. [30]	62.0 (55.0–62.5)		–		–		–16.4 ± 4.1	
LV strain normal vs reduced	62.5 (55.0–64.4)	57.5 (47.5–62.5)	–		–		–18.8 ± 2.7	–13.9 ± 4.1
Moody et al. [23]	60 (55–67)		40 (20–45)		–		–	
White vs non white ethnicity	58 (55–66)	62 (59–70)	40 (20–45)	49 (29–53)	–		–	
Goerlich et al. [27]	50.0 (50.0–62.5)		43.0 (37.3–48.0)		–		–	
RVSP > 40 vs ≤ 40 mmHg	58.8 (46.3–62.5)	62.5 (55.0–62.5)	43.0 (37.6–50.0)	42.0 (36.6–46.9)	–		–	
Evrard et al. [38]	–		–		–		–	
Covid-19 vs H1N1 Influenza	52 (44–61)	44 (28–59)	–		–		–	
Chen et al. [25]	55 (50–60)		–		–		–	
Schott et al. [45]	59 ± 10		–		–		–	
Lazzeri et al. [37]	55 ± 13		–		–		–	

Due to the size of the table, subgroups' interquartile ranges of Garcia-Cruz et al. paper [42] are not reported in the table. All the raw data are provided in the Supplementary Materials. EF, ejection fraction; EDD, end-diastolic diameter; ESD, end-systolic diameter; GLS, global longitudinal strain; ICU, intensive care unit; RV, right ventricle; P/F ratio, arterial oxygen partial pressure (PaO₂ in mmHg) to fractional inspired oxygen (FiO₂) expressed as a fraction; RVSP; right ventricle systolic pressure.

that a LV GLS > –15.2% [HR = 8.34 (95%CI 2.78–79.35); *p* < 0.001] and a RV GLS > –18.4% [HR = 6.22 (95%CI 1.51–25.67); *p* = 0.01] were independently associated to increased mortality [29]. Also, Lassen et al.

showed that RV longitudinal strain [HR = 1.64 (95%CI 1.02–2.66), *p* = 0.043, per 1% decrease], and GLS [HR = 1.20 (95%CI 1.07–1.35), *p* = 0.002, per 1% decrease] were significantly associated with increased

Table 3
Left ventricular (LV) diastolic function.

Authors and subgroup of patients	E wave velocity (cm/s)			E/A (ratio)		e' wave velocity (cm/s)			E/e' ratio		LA size (ml)			
Lariez et al. [31]	-			-		-			-		-			
Myocardial injury yes vs no	-			1.1 ± 0.4	1.2 ± 0.4	10 ± 3	13 ± 3	8 ± 3	6 ± 2	-				
Doyen et al. [44]	-			1.1 ± 0.3		10 ± 3			8 ± 3		-			
Myocardial injury yes vs no	-			1.1 ± 0.3	1.0 ± 0.3	9 ± 3	10 ± 3	8 ± 3	8 ± 2	-				
Van den Heuvel et al. [35]	-			-		-			7.2 (6.1–9.2)		-			
ICU admission yes vs no	-			-		-			-		-			
Zeng et al. [26]	-			-		-			-		-			
ICU admission yes vs no	-			-		-			-		31.0 ± 3.0	31.1 ± 2.9		
D'alto et al. [64]	-			-		-			-		-			
Non-survivors vs survivors	-			-		-			-		40 ± 5	38 ± 6		
Stobe et al. [18]	-			0.95 ± 0.3		-			8.6 ± 2.6		-			
Mild vs severe disease	-			1.15 ± 0.3	0.88 ± 0.2	-			6.7 ± 1.6	9.2 ± 2.6	-			
Barman et al. [15]	-			-		-			-		-			
Mild vs severe disease	-			1.20 ± 0.5	0.90 ± 0.3	-			-		34.6 ± 5.5	39.4 ± 5.5		
Deng et al. [21]	-			-		-			-		33.8 ± 4.2			
Mild vs severe disease	-			-		-			-		33 ± 4.0	34.3 ± 4.3		
Baycan et al. [29]	-			-		-			-		-			
Mild vs severe disease	90.6 ± 25.4	67.8 ± 13.6		1.0 ± 0.3	0.9 ± 0.3	-	-	-	9.1 ± 2.1	9.9 ± 2.9	34.5 ± 3.3	37.3 ± 5.4		
Szekely et al. [34]	-			-		-			-		-			
Mild vs moderate vs severe disease	66	64	55	1.12	1.08	0.77	8.7	7.8	7.5	10.5	10.6	9.0		
Kim et al. [40]	-			-		-			-		33 ± 9			
RV function normal vs impaired	-			-		-			-		37 ± 14	33 ± 8		
Garcia-Cruz et al. [42]	-			0.90 (0.75–1.36)		-			9.85 (5.5–12.2)		-			
P/F > 300; 201–300; 101–200; ≤100	-			0.69	0.89	1.11	0.90	-			5.1	6.3	10.0	12.0
Lassen et al. [16]	-			-		-			-		-			
Control vs Cases	-			0.90 (0.7–1.2)		1.0 (0.8–1.3)		-			8.5 (6.6–10.5)	8.5 (6.8–11.9)	-	
Goerlich et al. [30]	64 (52–77)			0.92 (0.76–1.1)		-			-		33 ± 9			
LV strain normal vs reduced	62 (56–81)			65 (51–83)	0.94 (0.82–1.3)	0.88 (0.70–1.0)	-			-		37 ± 14	33 ± 8	
Goerlich et al. [27]	-			-		-			9.8 (7.6–13.0)		-			
RVSP > 40 vs ≤ 40 mmHg	-			-		-			12.6 (8.7–15.7)	8.2 (6.6–9.9)	-			
Evrard et al. [38]	-			-		-			-		-			
Covid-19 vs H1N1 Influenza	-			-		-			7.3 (6.5–10.9)	7.8 (6.1–10.6)	-			

Due to the size of the table, subgroups' interquartile ranges of Garcia-Cruz et al. and Szekely et al. papers [34,42] are not reported in the table. All the raw data are provided in the Supplementary Materials. E/A waves, passive and active mitral inflow waves; LA, left atrium; e' wave, early diastolic mitral annular velocity; ICU, intensive care unit; RV, right ventricle; P/F ratio, arterial oxygen partial pressure (PaO₂ in mmHg) to fractional inspired oxygen (FiO₂) expressed as a fraction; RVSP; right ventricle systolic pressure,

mortality [16]. Finally D'Alto et al. showed that the ratio between TAPSE and pulmonary artery systolic pressure, was the only echocardiographic measurement independently predictive of mortality [HR = 0.026 (95% CI 0.01–0.579); p = 0.019].

4. Discussion

The main findings of this systematic review regarding echocardiographic findings in hospitalized, predominantly (68%) ICU COVID-19 patients can be summarised as follows: 1) a normal echocardiographic examination has been reported in about 50% of the enrolled subjects, and the largest report available [39] showed that the majority of subjects had non-specific patterns of ventricular dysfunction; 2) LVEF is usually not affected and has been reported higher than 50% in the most of the subjects; 3) although the assessment of LV diastolic function is complex, especially in critically ill patients, [46] a proper assessment of LV diastolic dysfunction in this population of patients is currently lacking; 4) it remains unclear whether overall RV dysfunction is associated to increased mortality; 5) we found insufficient information on fluid-responsiveness of these patients.

Importantly, it should be noted that our systematic review suffers from the own limitations of the selected studies. We were surprised to find a relatively low number of well-conducted large-scale studies in this field, considering the number of infected patients worldwide. Interestingly, the sole large study (n = 1216) accounting for one-third of the patients included in this systematic review provided

qualitative rather than quantitative echocardiographic data. Moreover, only seven studies with heterogeneous designs reported data on pure ICU patients, and none followed the recent PRICES statement and recommendation for reporting critical care echocardiography data [47,48]. This lack of accurate echocardiography data on COVID-19 patients may be multifactorial. We think that the hugely increased clinicians workload could partially explain this aspect under unprecedented pressure on the healthcare systems. This factor should also be paired with two other elements. First, there are specific technical difficulties in accurately performing bedside procedures (not only echocardiography) while wearing personal protective equipment [49]; second, human factors may affect the quality of echocardiographic assessment (i.e., fear of prolonged exposure to a patient with a highly transmissible disease).

Like other viral infections, COVID-19 may trigger a multi-systemic disease [7–10] and, among others, determine cardiac dysfunction [10,11,13]. The pathophysiologic mechanisms of cardiovascular impact in COVID-19 include cardiac complications directly related to myocardial involvement (favored by pre-existing systemic disease) or secondary to pulmonary damage, leading to a broad spectrum of LV and RV diastolic dysfunction [10,11,13]. These patterns may be associated or not with biochemical damage [50]. For instance, 9 studies [17,22,24,30,32,34,41,42,44] reported a low mean troponin I level of 0.07 ± 0.09 ng/ml (Supplementary Materials raw data) which, once ruled out acute coronary ischemia, may be considered of multifactorial origin [50]. As part of routine bedside clinical assessment,

Table 4
Right ventricular (RV) function and signs of hypovolemia.^a

Authors and subgroup of patients	TAPSE (mm)		RV systolic dysfunction (%)		RV dilation (%)		PAPS (mmHg)			IVC size (mm)		
Giustino et al. [41] Myocardial injury yes vs no	–	–	9	20	–	–	36 (28–46)			18 (14–21)		
Lariez et al. [31] Myocardial injury yes vs no	20 ± 4	20 ± 3	17	4	15	5	36 (28–47)			18 (14–21)		
Labbè et al. [22] Myocardial injury yes vs no	–	–	–	2.4	–	–	–			–		
Doyen et al. [44] Myocardial injury yes vs no	20 ± 5	–	–	4.1	–	0	26 ± 10			–		
Van den Heuvel et al. [35] ICU admission yes vs no	19 ± 5	23 ± 3	–	–	–	–	27 ± 9		22 ± 11		–	
Zeng et al. [26] ICU admission yes vs no	22 (20–27)	21 (19–26)	–	–	–	–	–			–		
Rath et al. [32] Non survivors vs survivors	24 (25–28)	–	–	–	–	–	34.5 ± 19.0		20.9 ± 4.0		–	
Bursi et al. [24] Non-survivors vs survivors	22 ± 5	–	13.7	48.9	–	–	–			–		
D'alto et al. [64] Non-survivors vs survivors	21 ± 6	23 ± 5	45.5	9.2	45.5	47.1	–			–		
Stockenhuber et al. [33] Non-survivors vs survivors	20 ± 4	–	–	–	–	–	–			–		
Stobe et al. [18] Mild vs severe disease	18 ± 3	21 ± 5	–	–	–	–	42 ± 12		30 ± 7		20 ± 3	
Barman et al. [15] Mild vs severe disease	19 ± 4	25 ± 4	–	–	–	–	26 ± 8.7		26 ± 9.2		21.1 ± 1.2	
Deng et al. [21] Mild vs severe disease	16.0 ± 0.56	–	–	–	–	–	26 ± 7.8		26 ± 9.2		–	
Baycan et al. [29] Mild vs severe disease	15.3 ± 0.81	17.5 ± 0.71	–	–	–	–	28.5 ± 7.3		35.5 ± 8.6		12.5 ± 2.6	
Li et al. [20] Severe vs critically severe	22 ± 3.2	–	–	–	–	–	28.7 ± 6.3		36.5 ± 10.4		–	
Szekely et al. [34] Mild vs moderate vs severe disease	22 ± 2.4	22 ± 3.5	–	–	–	–	29.8 ± 4.8		25.9 ± 13.5		14.0 ± 2.0	
Mahmoud-Elsayed et al. [17] RV function normal vs impaired	20.4 ± 2.4	17.6 ± 3.4	–	–	–	–	–		–		17.6 ± 3.8	
Kim et al. [40] RV function normal vs impaired	23 ± 5	23 ± 4	21 ± 7	–	–	–	39		38		50	
Garcia-Cruz et al. [42] P/F > 300; 201–300; 101–200; ≤100	23 ± 5	–	41	–	–	–	–			–		
Lassen et al. [16] Control vs Cases	23 ± 4	21 ± 6	26	80	–	–	–			–		
Rodríguez-Santamarta et al. [36] LVEF < 50% vs ≥ 50%	19 ± 5	–	–	–	–	–	–			–		
Goerlich et al. [30] LV strain normal vs reduced	20 ± 5	13 ± 2	–	–	–	–	32 (30–40)			17 (16–19)		
Moody et al. [23] White vs non-white ethnicity	18	18	20	20	–	–	32		28		43	
Evrard et al. [38] Covid-19 vs H1N1 Influenza	26 ± 5	20 ± 4	–	–	–	–	–			–		
Chen et al. [25] Schott et al. [45]	–	–	8.1	8.1	–	–	–			–		
Jain et al. [28] Dweck et al. [39]	–	–	33.3	3.2	16.7	6.5	–			–		
Lazzeri et al. [37]	19.0 ± 3.9	18.0 ± 3.7	–	–	–	–	–			–		
	20 ± 5	–	–	–	–	–	–			–		
	21 ± 5	20 ± 5	–	–	–	–	–			–		
	–	–	–	–	–	–	–			–		
	25 (23–29)	18 (16–22)	–	–	–	–	–			22 (19–26)		22 (21–24)
	–	–	17	10	–	–	33 (27–43)			–		
	–	–	27.7	81.7	–	–	–			–		
	–	–	40	15	–	–	–			–		
	–	–	30	15	–	–	–			–		
	–	–	–	–	–	–	51 ± 6			–		

Due to the size of the table, subgroups' interquartile ranges of Garcia-Cruz et al. paper [42] are not reported in the table. All the raw data are provided in the Supplementary Materials. TAPSE, tricuspid annular plane systolic excursion; PAPS, pulmonary artery systolic pressure; IVC, inferior cava vein; ICU, intensive care unit; RV, right ventricle; P/F ratio, arterial oxygen partial pressure (PaO₂ in mmHg) to fractional inspired oxygen (FiO₂) expressed as a fraction; LV, left ventricle; EF, ejection fraction.

^a Regarding the item of RV dilatation, the study of Rath et al. did not specify the criteria for RV dilatation, and therefore results should be interpreted with caution.

echocardiography has gained popularity in ICU because of its wide availability, high diagnostic yield, and prognostic value [51–57].

Overall, COVID-19 does not seem to affect LV performance in hospitalized patients significantly. LVEF is usually not (or at most mildly) affected. However, a more sophisticated strain assessment of myocardial function through GLS has shown normal values in 4 studies and mild impairment in 3 studies [18,30,35] (Table 2), suggesting that focal abnormalities may be present even when the global LVEF is preserved.

Data regarding LV diastolic dysfunction are of difficult interpretation due to the inconsistency of the reports. A precise assessment according to current guidelines [43] has not been described in the enrolled studies.

For instance, e' wave was evaluated only by three studies, showing on average borderline e' velocity. This finding may deserve more research since e' velocity describes an intrinsic relaxation property of the myocardium, and it could be affected at an early stage in patients developing sub-clinical myocarditis. Despite the possibly borderline values of e', most studies reported normal values of E/e' ratio (Table 3). Such conflicting findings leave questions open on the LV diastolic involvement, but the high prevalence of hypertension and diabetes in the enrolled patients may suggest that a pre-existing LV diastolic dysfunction could be already present at admission in many patients. It would be advisable to conduct longitudinal studies with serial echocardiography assessment

to ascertain the reversibility of viral-induced (transient) alteration of diastolic properties (i.e., increased e' velocity).

Conversely, despite finding more comprehensive data reporting on the RV function, the criteria adopted by the authors seem somewhat inconsistent and dis-homogenous, with variable cut-offs and definitions used (Supplemental Table S4 in the Supplementary Materials). RV dysfunction or failure in patients with COVID-19 pneumonia may be influenced by the increased incidence of pulmonary embolism and/or by micro-vascular pulmonary thrombosis associated with the disease [58,59]. However, the studies included did not report sufficient data in this regard to draw any conclusion. TAPSE was reported to be normal in most studies and borderline in one. However, several studies described a significant proportion of subjects with RV systolic dysfunction or dilatation (Table 3). Some studies reported that RV dysfunction might be directly related to adverse outcomes, and this association would not be surprising since it is well-known that ARDS induces uncoupling between RV function and afterload, eventually leading to RV failure and acute cor pulmonale. A recent large prospective study reporting data from 752 subjects with moderate-to-severe ARDS receiving protective ventilation showed that acute cor pulmonale was present in 22% of subjects and that disease severity was associated with in-hospital mortality [60]. In the setting of COVID-19 related ARDS, the prevalence of thromboembolic complications is high [61,62] and, as shown by the present literature summary, often associated with RV dysfunction. Along with the impact of mechanical ventilation on the right heart, serial echocardiographic assessment of RV function may be particularly helpful in therapy titration and assessing mechanical ventilation response.

Our systematic review also highlighted the absence of good-quality data regarding fluid management and fluid-responsiveness in this population of patients. Indeed, considering the primary pulmonary dysfunction responsible for the deterioration of these patients, it seems reasonable to implement a cautious approach in fluid management and keep these patients on the “dry side”. Such an approach may limit the degree of pulmonary edema, but the risks consequent to hypovolemia (hypoperfusion and ischemia) should not be underestimated [63].

This systematic review included studies enrolling different subject populations and vastly varying sample sizes. For instance, Dweck et al. reported qualitative data from 1216 subjects (32% of those included in this narrative review) collected from 69 countries across six continents and showed that 667 (55%) subjects had an abnormal scan. LV abnormalities were reported in 479 (39%) subjects, with a low incidence of ex-novo echocardiographic evidence of new myocardial infarction (3%), myocarditis (3%), and takotsubo cardiomyopathy (2%). LV impairment was classified as mild, moderate, or severe in 17%, 12%, and 9% of subjects, respectively. Qualitative RV abnormalities were reported in 397 (33%) subjects, with mild or moderate systolic impairment in 19% and severe systolic impairment in 6%. Notably, after the echocardiographic exam, no change in patients' management was reported in 67% of subjects [39].

4.1. Limitations

This study has several limitations due to the intrinsic limitations of the included studies. Due to the data's heterogeneity, it was not reasonable to perform a meta-analysis of specific echocardiographic measurements to correlate them to clinical outcomes. Second, most of the included studies adopted a qualitative assessment of both LV and RV function, limiting the data's comparability due to the evaluation's operator-dependency. Moreover, several factors may influence LV and RV function, including pre-existing cardiac or pulmonary diseases and the severity of COVID-19. Again, the lack of consistency in the severity scores adopted in the studies primarily affected data comparability.

Third, pre-existing cardiac conditions of patients are largely unknown, and accordingly, some reported findings may already be present before COVID-19. A longitudinal analysis with serial echo assessment

would provide more insights into the cardiovascular impact of COVID-19.

Unfortunately, with the current results, we cannot discriminate pre-existing cardiovascular risk associated with COVID-19 with the actual impact of the virus.

Fourth, all the studies enrolled a variable number of ICU patients, except for one in which this information is not provided [16]. However, this information is not clearly stated in some studies and may be just retrieved from the number of patients receiving invasive mechanical ventilation. Moreover, reported data are not analyzed according to ICU/non-ICU subgroup analysis, overall overlapping patients with different severity degrees of COVID-19.

Finally, we adopted a database combination search strategy, including MEDLINE®, EMBASE® and the Cochrane Controlled Clinical trials register, excluding different sources (i.e., Web of Science®). Although this choice should allow for reliable coverage of the published studies for the topic of interest, some studies might not have been identified.

Considering the need for a better characterization of myocardial function in COVID-19 patients, it is desirable the availability of high-quality echocardiographic data from an extensive international registry focused on ICU COVID-19 patients. In this regard, at least one multicentre study is currently ongoing (<https://clinicaltrials.gov/ct2/show/NCT04414410>).

5. Conclusions

There is growing literature regarding the echocardiographic features of COVID-19 infection. So far, studies have highly variable sample sizes and reported findings with a highly heterogeneous approach. Overall, quantitative data reporting is quite inconsistent, and the most extensive study available adopted qualitative criteria. The LVEF does not seem significantly affected, being reported as higher than 50% in most subjects, whereas LV diastolic function has not been properly assessed. RV dysfunction has been reported in higher figures but with variable criteria, making it difficult to establish its association with higher mortality.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

Conflict of interest for the present study: none declared. Conflict of interest unrelated to the present study in the last 36 months: Dr. Messina received travel expenses and registration for meetings and congresses from Vygon and Edwards. Prof. Cecconi is a consultant for Edwards Lifesciences, LiDCO and Cheetah Medical. Dr. Monge Garcia has received Honoraria and/or Travel Expenses from Edwards Lifesciences and Deltex Medical. He also received supply medical equipment (Doppler probes) in return for carrying out research works for Deltex Medical.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcrc.2021.05.010>.

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