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Echocardiographic Features of Cardiac Injury Related to COVID-19 and Their Prognostic Value: A Systematic Review

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Abstract

Background: The available information on the echocardiographic features of cardiac injury related to the novel coronavirus disease 2019 (COVID-19) and their prognostic value are scattered in the different literature. Therefore, the aim of this study was to investigate the echocardiographic features of cardiac injury related to COVID-19 and their prognostic value. **Methods:** Published studies were identified through searching PubMed, Embase (Elsevier), and Google scholar databases. The search was performed using the different combinations of the keywords "echocard*," "cardiac ultrasound," "TTE," "TEE," "transtho*," or "transeso*" with "COVID-19," "sars-COV-2," "novel corona, or "2019-nCOV." Two researchers independently screened the titles and abstracts and full texts of articles to identify studies that evaluated the echocardiographic features of cardiac injury related to COVID-19 and/or their prognostic values. **Results:** Of 783 articles retrieved from the initial search, 11 (8 cohort and 3 cross-sectional studies) met our eligibility criteria. Rates of echocardiographic abnormalities in COVID-19 patients varied across different studies as follow: RV dilatation from 15.0% to 48.9%; RV dysfunction from 3.6% to 40%; and LV dysfunction 5.4% to 40.0%. Overall, the RV abnormalities were more common than LV abnormalities. The majority of the studies showed that there was a significant association between RV abnormalities and the severe forms and death of COVID-19. **Conclusion:** The available evidence suggests that RV dilatation and dysfunction may be the most prominent echocardiographic abnormality in symptomatic patients with COVID-19, especially in those with more severe or deteriorating forms of the disease. Also, RV dysfunction should be considered as a poor prognostic factor in COVID-19 patients.

Keywords

echocardiography, right ventricle, left ventricle, prognosis, COVID-19

Introduction

The current Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be one of the most serious public health challenges facing the world today.[1] Based on the available evidence, the clinical spectrum of the COVID-19 is varied, ranging from self-limiting respiratory symptoms to severe pneumonia, multi-organ dysfunction, and death.[2,3]

Given the considerable frequency of cardiac manifestations reported among patients with COVID-19, it has been supposed that SARS-CoV-2 may directly or indirectly cause acute cardiac injury, leading to alterations of cardiac structure and function.[4] Recent studies have utilized echocardiography, as an available, non-invasive, and informative diagnostic tool, to identify the features of cardiac injury related to the COVID-19.While identifying the potential role of the echocardiographic findings as a prognostic factor in COVID-19 patients, some of these studies have also evaluated the associations of them with the biomarkers of cardiac injury.

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However, the available information on the echocardiographic features of cardiac injury related to the COVID-19 and their association with the poor outcomes and biomarkers of cardiac injury, inflammation, and thrombosis is scattered in the literature, making it difficult to utilize this information for the clinical decision making. Therefore, this systematic review aimed to provide a concise and cohesive summary of the most important findings from each available literature.

Methods

This systematic review was conducted and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Ethical approval and informed consent were not required for this study as it was a systematic review of previously published studies.

In this systematic review, we included studies that assessed the echocardiographic features of cardiac injury related to the COVID-19 and their association with the poor outcomes and biomarkers of cardiac injury, inflammation, and thrombosis.

Search

The electronic databases, such as Pubmed, Embase, and Google Scholar were searched between June 8, 2020 and July 29th, 2020, using the terms "echocard*," "cardiac ultrasound," "TTE," "TEE," "transtho*," or "transeso*" combined with "COVID-19," "sars-COV-2," "novel corona," or "2019-nCOV."

Additionally, to identify the additional studies, we checked the reference lists of all included studies. All retrieved articles were added to EndNote X8.2 reference management software, and duplicates were deleted.

Study Inclusion

Two researchers [ESh & HR] independently reviewed the titles and abstracts of retrieved studies to identify the relevant studies. In the case of disagreement, a third researcher was consulted (NSh or ZKh). Finally, the full texts of the identified articles were reviewed by 2 independent reviewers in the second phase of the review (NSh & HR). Any disagreements were resolved by discussion.

Inclusion Criteria

Articles that met the following criteria were included in the study: (1) (1) observational studies, including cross-sectional studies and cohort studies; (2) studies that included COVID-19 out/inpatients older than 18 years;(3) studies written in English; (4) published after January 2020 in a peer-review journal; and (5) studies addressing at least one of the following issues: I) the echocardiographic features of cardiac injury related to COVID-19, II) prognostic value of identified echocardiographic abnormalities and/or III) associations of these abnormalities with biomarkers of cardiac injury, inflammation, and thrombosis.

Exclusion Criteria

The exclusion criteria were specified as follows: (1) studies with less than 30 patients; and (2) studies focusing on patients with pre-existing cardiac disease.

Data Extraction

Two independent researchers [NSh& HR] extracted data from the full texts of included studies into a standardized Excel (Microsoft Corporation) form. The following information was obtained: first author's name, country, study design, sample size, age, sex, and main findings. The extracted data are presented in the tables.

Quality Assessment

Quality assessment was performed by 2 researchers using the Newcastle– Ottawa scale (NOS), containing 9 items, for the cohort studies and using the Prevalence Critical Appraisal Instrument (PCAI), containing 10 items, for the cross-sectional studies.[5] In Newcastle– Ottawa scale, the total score ranged from 0 to 9 and was categorized into 3 groups: Low quality "0-3," moderate quality "4-6," and high quality "7-9." In the Prevalence Critical Appraisal Instrument (PCAI), the total score ranged from 1 to 10. During the quality assessment of the included studies, any disagreements were resolved by discussion or a third researcher.

Results

Study Selection Process

A total of 887 articles were identified in the initial search. After the removal of duplicates ($n = 104$) and those not meeting the inclusion criteria (by title/abstract: $n = 737$, full text: $n = 35$), 11 eligible articles(including 8 cohort studies and 3 cross-sectional studies) were entered into this review (Figure 1).

Study Characteristics

Table 1 presents the characteristics of the included studies. All 11 articles were involved in Covid-19 hospitalized patients who underwent transthoracic echocardiography (TTE). The studies were performed in different countries; one of them was an international survey, including patients from 69 countries across 6 continents.[6]

The mean/median age of patients fell in the seventh decade of life with a male predominance in the majority of studies. In all but one study, the sample size was small, ranged from 30 to 200; the exception was the international study, including 1,216 patients.[6]

Six out of 11 studies provided data on the length of time to the echocardiography.[7-11,13] Two studies reported that echocardiography was performed within the first 24 h of admission for each patient.[8,13]

Six studies reported the percentage of patients receiving mechanical ventilation at the time of echocardiography,[7,8,13-16] It varied from 0.0% (non-ICU population) to 100% (all intubated)[16] of the study population in different studies.

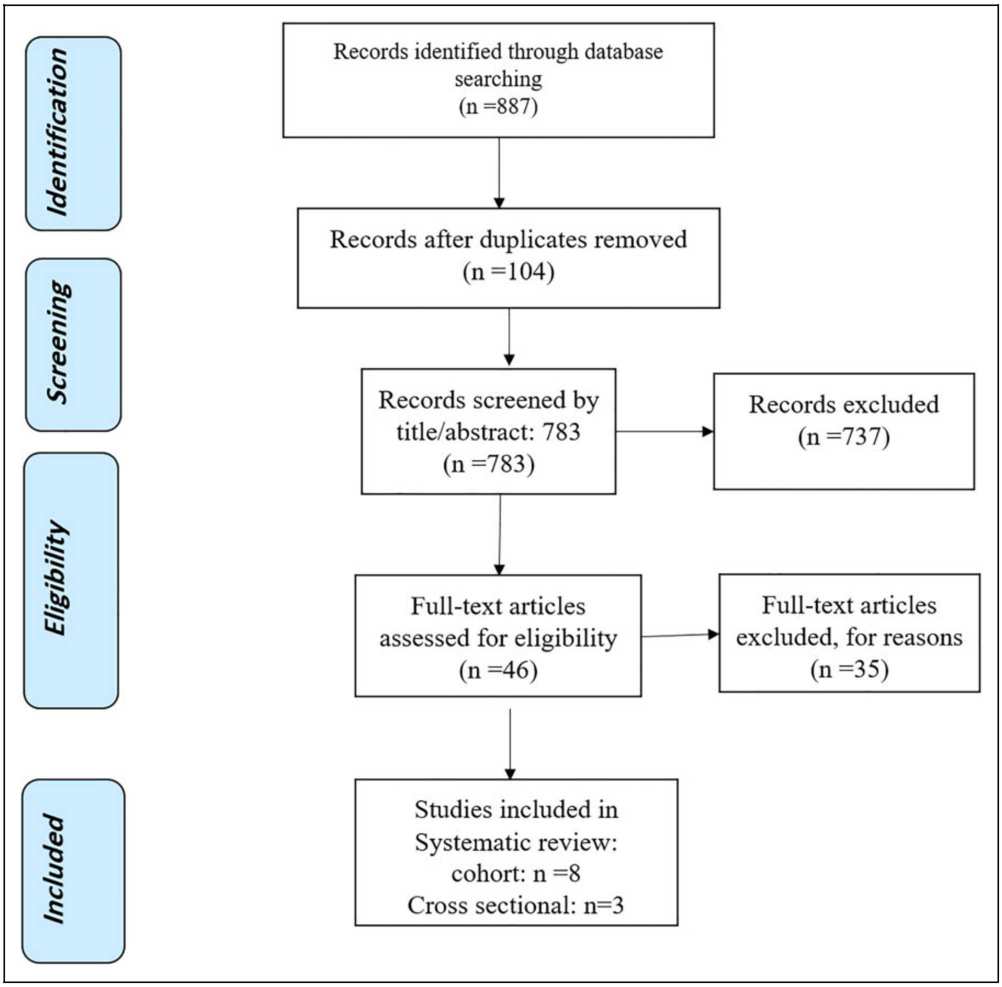

Figure 1. PRISMA flowchart of literature search and selection process.

All 8 cohort studies had a quality score higher than 6, and 3 cross-sectional studies conducted by Dweck et al[6] Jain et al[13] Sollazzo et al[16] had quality scores 9, 8, and 7, respectively (Table 2).

Echocardiographic Abnormalities

As shown in Table 3, investigators assessed the abnormalities of the right and left ventricular (RV and LV) using different echocardiographic indices.

Rates for echocardiographic abnormalities in structure and function varied in included studies as follow: RV dilatation from 15.0% to 48.9%; RV dysfunction from 3.6% to 40%; and LV dysfunction from 5.4% to 40.0%. The rate of LV dilatation was only reported by 2 studies conducted by Mahmoud-Elsayed et al[8] (in 4% of patients) and Dweck et al[6] (in 5% of patients).

Except for 2 studies conducted by Li et al[10] and Pagnesi et al[7] that only addressed RV dysfunction, 9 studies have evaluated echocardiographic abnormalities of right and left side of the heart, of which 6 had evaluated RV dysfunction (± dilatation) and LV dysfunction[8,11-14] and 3 studies focused on RV dilatation and LV dysfunction.[9,15,16] (Table 3).

Dweck et al[6] reported a similar dysfunction rate for RV and LV (31% and 38%, respectively) in their international study; however, they found a higher rate of RV dysfunction than LV dysfunction (33% vs. 25%, respectively) after excluding those with pre-existing cardiac diseases.

Of the remaining studies addressed both RV and LV abnormalities (n = 8), 4 studies showed a higher abnormality rate of RV (dilatation/dysfunction) than LV.[8,9,11,13] Three studies found a roughly similar abnormality rate,[12,15,16] of which 2 reported only RV dilatation,[15,16] and the other one focused on RV dysfunction.[12]

Finally, one study (sample size = 51), focusing on the function of RV and LV, found a higher dysfunction rate of LV than RV (27% vs. 10%).[14]

The Prognostic Values of Echocardiographic Abnormalities in COVID-19

Table 4 presents the main findings of each included study regarding the association of echocardiographic abnormalities with poor outcomes of COVID-19. Except for the studies conducted by den Heuvel et al[14] and Pagnesi et al[7] all studies found a significant association between RV dysfunction with severe

Table 1. Characteristics of the Included Studies.

	Author	Country	Study type	Sample size	Diagnosis of COVID-19	Age (year) mean ± SD/median (IQR)	Male, N (%)	Length of time to echocardiography Median (IQR)	Being ventilated N (%) At the time of echo.	Being ventilated N (%) During hospitalization
1	Dweck et al[6]	International*	Cross sectional	1,216	NR	62 (52–71)	844 (70%)	NR	NR†	NR.
	Pagnesi et al[7]	Italy	Prospective cohort	200	According to the interim guidance of WHO	62 (52–74)	131 (66%)	7 (3–13) days	0 (0.0%)‡	7 (3.5%)
2	Mahmoud-Elsayed et al[8,§]	UK.	Retrospective cohort	74	PCR-RT	59 ± 13	58 (78%)	5 (3-10) days	58 (78%)	61 (82%)
3	Szekely et al[9]	Israel	Prospective cohort	100	According to the interim guidance of WHO	66 ± 17	63 (63%)	Within first 24 h of admission	NR.	10 (10%)
4	Li et al[10]	China	Prospective cohort	120	PCR-RT	61 ± 14	57 (48%)	7(3-10) days	NR	15 (12.5%)
5	Rath et al[11]	Germany	Prospective cohort	123	PCR-RT	68 ± 15	77 (63%)	Within first 24 h of admission	NR	49 (39.8%)
6	Deng et al[12]	China	Retrospective cohort	112	According to the interim guidance of WHO	65 (49-70.8)	57 (51%)	NR	NR	28 (25.0%)
7	Jain et al[13]	USA	Cross sectional	72	PCR-RT	61 (50-70)	52 (72%)	3 days (NR)	40 (55.6%)	NR.
8	Van den Heuvel et al[14]	Netherland	Retrospective cohort	51	PCR-RT (in 92%)	63 (51–68)	41 (80%)	NR	17 (33%)	NR.
9	Argulian et al[15]	USA	Retrospective cohort	105	NR	66.0 ± 14.6	72 (65%)	NR	31 (30%)	NR.
10	Sollazzo et al[16]	Italy	Cross sectional	30	NR	NR	NR	NR	30 (100%)	NR

NR: Not reported. PCR-RT: Polymerase chain reaction- Reverse-transcriptase. IQR: Interquartile range. WHO: World Health Organization.
*Data was collected from 69 countries across 6 continents.
†Overall, 726 (60%) of patients were admitted at the critical care.
‡Non-ICU population were included.
§Patients Without previously abnormal echocardiography were included.

Table 2. Quality of the Included Cohort Studies.

N	Study	Selection 1	2	3	4	Comparability (**)	Outcome a	b	c	Total Of 9 scores
	Pagnesi et al[7]	*	*	*	*	*	*	*	*	8
1	Van den Heuvel et al[14]	*	*	*	*	–	–	*	*	6
2	Argulian et al[15]	*	*	–	*	*	*	*	*	7
3	Mahmoud-Elsayed et al[1]	*	*	*	*	*	*	*	*	8
4	Szekely et al[2]	*	*	*	*	**	*	*	*	9
5	Li et al[3]	*	*	*	*	*	*	*	*	8
6	Rath et al[11]	*	*	*	*	*	*	*	*	8
7	Deng et al[12]	*	*	*	*	*	*	*	*	8

1. Representativeness of exposed cohort (⋆).
2. Selection of non-exposed cohort (⋆).
3. Ascertainment of exposure (⋆).
4. The Outcome of Interest Was Not Present at Start of Study (*).
a) Assessment of outcome (⋆).
b) Enough follow-up to occur outcomes (*).
c) Adequacy of follow up (⋆).

Table 3. Cardiac Function Based on Echocardiography Findings in Patients With COVID-19.

N	Author	Right ventricle: % (N) Dilatation	Right ventricle: % (N) Dysfunction	Left ventricle: % (N) Dilatation	Left ventricle: % (N) Dysfunction	Definition of abnormalities
1	Dweck et al[6]	15% (181)	31% (382)	5% (66)	38% (445)	NR.
2	Pagnesi et al[7]	NR	14.5% (29)	NR	NR	RV dysfunction: TAPSE) of <17 mm or tissue Doppler imaging S wave (S' wave) of <9.5 cm/s
3	Mahmoud-Elsayed et al[8]	41% (30)	27% (20)	4% (3)	11% (8)	RV dilatation: RV basal diameter >41 mm RV dysfunction: FAC <35% *or* a TAPSE <17 mm LV systolic function: Visual assessment
4	Szekely et al[9]	39% (39)*	NR	NR	Systolic: 10% (10) Diastolic: 16% (16)	RV dilatation/dysfunction: NR LV dysfunction: LVEF below 50%
5	Li et al[10]	NR	33% (40)	NR	NR	RV dysfunction: RVLS ranged 10.3 to 20.5%
6	Rath et al[11]	48.9% (46)	13.7% (13)	NR	15% (19)	LV dysfunction: EF $\leq$ 50% RV dysfunction: Visual assessment
7	Deng et al[12]	NR	3.6% (4)	NR	5.4% (5)	LV dysfunction: EF $\leq$ 50% RV dysfunction: TAPSE < 16 mm
8	Jain et al[13,†]	18% (11)	46% (29)	NR	36.7% (25)	LV dysfunction: EF $\leq$50% RV dysfunction: Semi-quantitatively was assessed
9	Argulian et al[15]	30.4% (32)	NR	NR	31.4% (33)	RV dilatation: basal diastolic RV diameter > 4.1 cm in the apical view and/or basal right-to-left ventricular diameter ratio of $\geq$0.9 in the apical 4-chamber view, and confirmed by visual RV assessment. Other abnormalities: NR.
10	Sollazzo et al[16,‡]	40% (12)	NR	NR	40% (12)	NR.
11	den Heuvel et al[14]	NR.	10% (5)	NR	27% (14)	LV dysfunction: LVEF < 52% and/or GLS > –18% RV dysfunction: TAPSE < 17 mm and/or RV S' < 10cm/s

GLS: global longitudinal strain. FAC: fractional area change. EF: Ejection fraction. LV: Left ventricular, LVEF: Left ventricular ejection fraction. NR: Not Reported. RV: Right ventricular. TAPSE: tricuspid annular plane systolic excursion. RVS': right ventricular systolic excursion velocity.
*RV dilatation with or without dysfunction.
†Patients underwent TTE mainly due to major acute cardiovascular event (45.8%) or hemodynamic instability (29.2%).
‡Of 12 patients with a LV dysfunction, 4 had a takotsubo Syndrome and 8 had a myocardial injury. All patients with RV dilatation had also acute pulmonary hypertension.

or worsening forms of the disease,[9,12] Pulmonary Embolism (PE),[8] ARDS,[10] and/or mortality[10-12] (All p-values < 0.05). Also, in a study conducted by Argulian et al[15] RV dilation was a significant predictor of in-hospital mortality in COVID-19 patients, considering the confounding effect of mechanical ventilation and vasoactive medication use. (Odds ratio (95% confidence interval): 4.5 (1.5 to 13.7); $p = 0.005$).

Szekely et al[9] also observed that acute RV dysfunction is more prevalent than acute LV systolic dysfunction in patients experiencing clinical deterioration.

Table 4. Prognostic Value of Echocardiographic Findings in COVID-19.

	Author	Quantitative assessment	Abnormality on echo.		Outcome	Finding
1	Dweck et al[6]	In patients with COVID-19 without pre-existing cardiac disease, in contrast to LV dysfunction, moderate (OR (95% CI: 2.34 (1.32-4.29)) and severe (3.19 (1.73-6.10) forms of the disease were significantly associated with RV dysfunction	RV dysfunction LV dysfunction		Severity of disease	+ NS
2	Pagnesi et al[7]	There were non significantly difference in patients with or without RVD regarding the rate of the primary endpoint (17.2 vs 11.7%; p = 0.404) and of all-cause mortality (13.8 vs 8.8%; p = 0.489).	RV dysfunction		ICU admission Need to invasive mechanical Death	NS NS NS
3	Mahmoud-Elsayed et al[8]	– PE, detected on CT angiography, occurred more frequently in patients with RV systolic dysfunction than others (20.5% vs. 2.0%, p = 0.02) – A higher percentage of patients with impaired RV function (n = 20) had moderate to high probability of pulmonary hypertension than others (55% vs. 26% , p = 0.006)	RV dysfunction		– PE – Pulmonary hypertension	+ +
4	Szekely et al[9]	– PAT (ms) was shorter in patients with Grade* 2& 3 of disease [mean (SD), Grade 1: 102(30) , Grade 2: 81(24), Grade 3: 86(31), p = 0.01] – DVT was detected in 5 out of the 12 patients with RV deterioration at follow-up. Besides, 2 out of 7 patients without DVT underwent CT angiography, of whom one diagnosed by PE.	RV dysfunction Acute RV dysfunction LV dysfunction Acute LV dysfunction		– Clinical deterioration – Severity of disease – Clinical deterioration – Severity of disease – Clinical deterioration – Clinical deterioration	+ + + NS NS. NS
5	Li et al[10]	– TAPSE, nm (HR (95% CI): 0.88(0.78-0.99), RV-FAC, % (0.90 (0.83-0.98), RVLS (1.33(1.15-1.53)) all were associated with death. – Compared to patients in the highest tertiles, those in the lowest RVLS tertile more frequently experienced DVT (62% vs. 30%, P = 0.003), ARDS (52% vs. 25%, p = 0.011), acute heart injury (55% vs. 12%, p < 0.001), or death (32% vs. 0.0%, p < 0.001). – Among RV function parameters, RVLS was the strongest predictor of death.	RV dysfunction LV dysfunction		– Death – ARDS – Acute heart injury – DVT – Death	+ + + + NS
6	Rath et al[11]	– Patients with impaired LVEF and RV function had a worse cumulative survival than those with normal LVEF and RV-function. [P of log rank test < 0.001] – Patients with impaired LVEF (vs. normal LVEF), and impaired RV-function (vs. normal RV-6function) had a higher mortality. [both P of log rank test < 0.001]	RV dysfunction LV dysfunction		– Death – Worse cumulative survival – Death – Worse cumulative survival	+ + + +
7	Deng et al[12]	– Patient with severe disease vs. those with non-severe disease had a higher frequency of LV dysfunction (2.2% vs. 7.5%) and RV dysfunction (TAPSE < 16 mm: 6.0% vs. 0.0%) – Patient with composite endpoint (including the admission to ICU, or receiving mechanical ventilation or ECMO, or death) vs. others: – LV dysfunction: 16.1% vs. 1.2%, P < 0.01 – RV dysfunction (TAPSE < 16 mm): 12.9% vs. 0.0% , P < 0.01) – All patient with TAPSE < 16 mm (n = 4) was detected in those with severe form of disease	RV dysfunction LV dysfunction		– Severity of disease – omposite endpoint – Severity of disease – Composite endpoint	+ + + +
8	Van den Heuvel et al[14]	– Patients admitted at ICU had a worse GLS than others (median (IQR): –19.7 (–21 to -19.1) vs. –17.7 (–18.5 to –16.4), P = 0.005) – There were no significant differences between 2 groups regarding other parameters of LV (LVEF) and RV functions (TAPSE and RV S')	RV dysfunction LV dysfunction	# TAPSE # RV S' # GLS #LVEF	– Admission to ICU	NS NS. + NS
9	Argulian et al[15]	In the multivariate analysis, adjusted for mechanical ventilation and vasoactive medication use, RV dilatation was significantly associated with mortality (OR (95% CI): 4.5 (1.5 -13.7); p = 0.005).	RV dilatation		– Death	+

*Grade 1: without need to oxygen, Grade 2: need to non-invasive oxygen Grade 3: need to invasive mechanical ventilation.

ARDS: Acute respiratory distress syndrome. AUC: area under the curve. CI: Confidence Interval. CT: computed tomography. DVT: Deep vein thrombosis. EF: Ejection fraction. ECMO: extracorporeal membrane oxygenation. GLS: Global longitudinal strain. HR: hazard ratio. ICU: intensive care unit. LV: Left ventricular, LVEF: Left ventricular ejection fraction. PAT: Pulmonary acceleration time. PE: Pulmonary Embolism. RV: Right ventricular. RVLS: Right ventricular longitudinal strain. RV-FAC: Right ventricular fractional area change. RV S': right ventricular systolic excursion velocity. TAPSE: tricuspid annular plane systolic excursion.

Table 5. Association of the Echocardiographic Findings With the Biomarkers of Cardiac Injury, Inflammation and Thrombosis in COVID-19 Patients.

N	Author	Quantitative assessments	Abnormality on echocardiography	Biomarker	Finding
1	Dweck et al[6]	– In patients without preexisting cardiac disease, both elevated troponin (OR (95% CI: 1.69 -1.13-2.53)) and BNP (2.96 (1.75-5.05) were significantly associated with LV dysfunction but not with RV dysfunction (trop: 1.3 (0.86 -1.95), BNP: 1.1(0.63 -1.88)	RV dysfunction	– Troponin	NS
				– BNP	NS
			LV dysfunction	– Troponin	+
				– BNP	+
	Pagnesi et al[7]	Patients with RVD had lower levels of C reactive protein (CRP) ($p = 0.019$) and higher levels of hs-troponin T ($p = 0.006$), creatine phosphokinase (CPK) ($p = 0.010$) and NT-proBNP ($p = 0.011$).	RV dysfunction	– Troponin	+
				– NT-pro BNP	+
				CPK	+
				CRP	–
2	Mahmoud-Elsayed et al[8]	– RV systolic dysfunction was associated with elevated D-dimer ($\rho = -0.34$, $p = 0.003$) and CRP ($r = -0.23$ $p = 0.045$), but not with hs-troponin.	RV dysfunction	– D-dimer	+
				– CRP	+
				– Troponin	NS
3	Szekely et al[9]	– Troponin level was associated with indices of RV function, also with LV diastolic function. – Also, patients with shorter AT (<100 ms) had higher levels of D-dimer, BNP, troponin-I, and CRP	RV dilatation (based on AT)	– D-dimer	+
				– BNP	+
				– Troponin	+
				– CRP	+
			RV dysfunction	– Troponin	+
			LV diastolic dysfunction	– Troponin	+
4	Li et al[10]	– Compared with patients in the highest tertiles, those in the lowest RVLS tertile were more likely to have a higher D-dimer, mg/L [Median (IQR): 1.84 (0.83,6.13) vs. 0.76 (0.35,2.64), $P = 0.053$] and CRP, mg/L [29.8(3.7,64.2) vs. 11.2(1.1,48.7), $p = 0.053$)] – There were no significant differences among the tertiles of RVLS regarding CPK-MB, hs- troponin-I, BNP.(all p values >0.05)	RV dysfunction (based on RVLS)	– D-dimer	+
				– CRP	+
				– CPK-MB	NS
				– BNP	NS
				– Troponin	NS
5	Rath et al[11]	– At admission, troponin I and NT pro-BNP levels were associated with LEVF (rho = – 0.367, $p < 0.001$ and rho = – 0.485, $p < 0.001$, respectively) and RV-FAC (rho = – 0.442, $p < 0.001$ and rho = – 0.304, $p = 0.006$, respectively). – In contrast, D-dimers level was associated with neither LVEF (rho = – 0.155, $p = 0.116$) nor RV-FAC (rho = – 0.103, $p = 0.321$) LVEF	RV dysfunction (based on RV-FAC)	– Troponin	+
				– NT pro BNP	+
				– D-dimer	NS
			LV dysfunction	– Troponin	+
				– NT pro BNP	+
				– D-dimer	NS
6	Jain et al[13]	– LVEF had an inverse association with hs-troponin (rho = -0.34, $p = 0.006$) and non-significant association with NT-pro BNP (rho = -0.29, $p = 0.056$).	LV dysfunction	– Troponin	+
				– NT pro BNP	NS
7	Van den Heuvel et al[14]	– There were no significant association between elevated Troponin and BNP with parameters LV and RV functions (all p- value >0.05)	RV dysfunction	– Troponin	NS
				– BNP	NS
			LV dysfunction	– Troponin	NS
				– BNP	NS

AT: acceleration time. BNP: brain natriuretic peptide. CK-MB: creatinine kinase MB CRP: C-reactive protein FAC: fractional area change. LV: Left ventricular, LVEF: Left ventricular ejection fraction. RV: Right ventricular. RVLS: Right ventricular longitudinal strain. RV-FAC: Right ventricular fractional area change.

Li et al[10] found that among parameters assessed for RV function, right ventricular longitudinal strain (RVLS) was the strongest predictor of death. Based on their findings, -23% ($AUC = 0.87$; $P < 0.001$) was the best cutoff value of RVLS for the prediction of adverse clinical outcomes.

Three out of 6 studies evaluating the prognostic value of LV dysfunction,[9-12,14] including the international survey conducted by Dweck et al[6] showing no significant association between LV dysfunction with severity and death of COVID-19.

Association of Echocardiographic Abnormalities With Biomarkers

The included studies showed a significant association between elevated levels of hs-troponin[7,9,11] brain natriuretic peptide (BNP),[7,11] creatinine kinase MB (CK-MB),[10] C-reactive protein (CRP),[8,10] and D-dimer[8,10] with RV dysfunction and/or dilatation. Also, some of these biomarkers, including hs-troponin[9,11,13] and BNP,[11] were also associated with LV dysfunction (Table 5).

Discussion

Our findings suggest that dilatation and dysfunction of RV are the most prominent echocardiographic abnormality observed in patients with COVID-19, especially in those with a more severe or deteriorating form of the disease. Also, some studies have revealed that RV abnormalities may be associated with the poor outcomes of COVID-19.

Most of the included studies, using different echocardiographic indices of RV function, have shown that RV dilatation and dysfunction are the predominant echocardiographic abnormalities in COVID-19 patients with cardiac symptoms. However, some studies failed to observe this higher abnormality rate of RV than LV in COVID-19 patients. However, in an international study, Dweck et al[6] used the data from a large sample size of COVID-19 patients and showed a roughly similar dysfunction rate for RV and LV, after excluding those with pre-existing cardiac diseases. Also, they found a higher rate of RV dysfunction rather than LV dysfunction.

Furthermore, one study found a higher dysfunction rate of LV than RV.[14] Compared to other studies, this study had used different criteria (LVEF < 52% and/or GLS > –18%) that could result in higher sensitivity for detecting LV dysfunction. On the other hand, they have unexpectedly noted a better RV function (based on TAPSE and RV S' indices) in patients with PE than those without PE, that makes the findings questionable.

Our findings are in line with previous studies suggesting that RV dysfunction frequently occurs in patients with respiratory-related diseases such as flu[17-19] and ARDS.[20,21]

The potential mechanisms of impaired RV function and structure occurring in COVID-19 are unclear; however, parenchymal and vascular lung injury induced by the virus could play a key role in this disease.[22] In other words, the occurrence of pulmonary edema, reduced lung compliance, microvascular thrombosis, and acute severe hypoxemia in COVID-19 could increase pulmonary vascular resistance and/or pressure, leading to an acute increase in RV afterload.[23]

LV dysfunction, mainly diastolic, has also been observed in COVID-19 patients, but it is uncommon. Here, cardiovascular complications directly or indirectly induced by Sars-cov2 infection, such as myocarditis, coronary artery disease, arrhythmia, pericarditis, endocarditis, may lead to LV dysfunction.[18,22]

Some of the included studies revealed that the presence of RV dilatation and dysfunction might be associated with biomarkers of cardiac injury such as CPC-MB, troponin, and BNP in COVID-19. As elevated levels of troponin, cpk-MB, and BNP may result from a various range of cardiac injuries occurring at different stages of the COVID-19,[18] complementary imaging examinations such as echocardiography are highly recommended for more accurate diagnosis, prognosis evaluation, and clinical decision making.[18]

However, a sequence of events may explain the association between RV dysfunction and cardiac injury biomarkers cpk-MB, troponin, and BNP. Increased RV systolic pressure caused by acute RV pressure overload gradually results in RV dysfunction, that, in turn, leads to reduced cardiac output and systemic blood pressure, followed by a decrease in coronary blood flow to the RV, leakage of cardiac biomarkers, and more decrease in RV function.[9]

Given the association of the cardiac injury biomarkers with the most common echocardiographic abnormality, the acute RV dysfunction should be considered as the most probable mechanism for elevated levels of the cpk-MB, troponin, and BNP in COVID-19 patients.[9]

Additionally, our review revealed that the presence of RV dysfunction is associated with inflammatory and thrombotic biomarkers like elevated levels of D-dimer and CRP. There is growing evidence that COVID-19 is associated with the imbalance of coagulation and inflammatory pathways, indicating elevated levels of thrombotic and inflammatory factors.[24,25] This phenomenon can lead to the development of micro-thrombus in the pulmonary vasculature, increasing the risk of thromboembolic complications, and subsequent RV dysfunction in these patients.[26]

Our review also showed the prognostic value of RV dysfunction in COVID-19 patients. It has been long known that RV dysfunction is associated with significant morbidity and mortality in cardiovascular disease and ARDS.[27,28] The mechanism of this association is unclear. However, based on the multifactorial nature of RV dysfunction, Orde et al argued that RV dysfunction is a marker of disease severity, associated with poor outcomes.[29]

In addition, the worsening of the impaired RV parameters on subsequent echocardiogram has been reported in patients who experienced clinical deterioration that may be explained by increased pulmonary resistance.[9]

Obviously, this study has some limitations. First, most of the included studies had have had very small sample sizes. Second, the included studies utilized the different indices for assessing RV function and defining impaired RV function. Third, all included studies were conducted on hospitalized patients with cardiac-related symptoms, limiting the generalizability of their findings to the entire COVID-19 patients. However, this is the first systematic review of studies examining echocardiographic features of cardiac injury related to the COVID-19 and their prognostic impact.

Conclusions

Impaired RV function is probably the most prominent echocardiographic abnormality in patients with COVID-19, especially in those with a more severe or deteriorating form of the disease. Also, RV dysfunction may be associated with the poor prognosis of COVID-19 and biomarkers of cardiac injury.

Therefore, comprehensive echocardiography assessment of the right side is recommended in COVID-19 patients with cardiac-related symptoms for more accurate diagnosis, prognosis evaluation, and clinical decision making.

Authors' Note

Ehsan Shahrestanaki, and Hadith Rastad are equally contributed. N-Sh and HR had the idea for and designed the study. RS and E-Sh developed the search strategy and selection process. Sh-A extracted the data. HR, E-Sh and Z-Kh did synthesis and all authors have drafted the paper. Also, all authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published.

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References

1. Harapan H, Itoh N, Yufika A, et al. Coronavirus disease 2019 (COVID-19): a literature review. *J Infect Public Health*. 2020;13(5):667-673.
2. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;34:101623.
3. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *J Gen Intern Med*. 2020;35(5):1542-1549.
4. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. *J Cardiovasc Electrophy*, 2020;31(5):1003-1008.
5. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *Int J Health Policy Manag*. 2014;3(3):123-128.
6. Dweck MR, Bularga A, Hahn RT, et al. Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging*. 2020:21(9):949-958.
7. Pagnesi M, Baldetti L, Beneduce A, et al. Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. *Heart*. 2020;106(7):1324-1331.
8. Mahmoud-Elsayed HM, Moody WE, Bradlow WM, et al. Echocardiographic findings in COVID-19 pneumonia. *Can J Cardiol*. 2020;36(8):1203-1207.
9. Szekely Y, Lichter Y, Taieb P, et al. The spectrum of cardiac manifestations in coronavirus disease 2019 (COVID-19)—a systematic echocardiographic study. *Circulation*. 2020;142(4):342-353.
10. 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(11):2287-2290.
11. Rath D, Petersen-Uribe Á, Avdiu A, et al. Impaired cardiac function is associated with mortality in patients with acute COVID-19 infection. *Clin Res Cardiol*. 2020;109(12):1491-1499.
12. Deng Q, Hu B, Zhang Y, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. *Int J Cardiol Heart Vasc*. 2020;311:116-121.
13. Jain SS, Liu Q, Raikhelkar J, et al., Indications and findings on transthoracic echocardiogram in COVID-19. *J Am Soc Echocardiogr*. 2020;33(10):1278-1284.
14. van den Heuvel FMA, Vos JL, Koop Y, et al. Cardiac function in relation to myocardial injury in hospitalised patients with COVID-19. *Neth Heart J*. 2020;28(7-8):410-417.
15. Argulian E, Sud K, Vogel B, et al. Right ventricular dilation in hospitalized patients with COVID-19 infection. *JACC Cardiovasc Imaging*. 2020;13(1):2459-2461.
16. Sollazzo V, Dibiase F, La Torre PP, Galante D, Pellegrino ML, Placentino M, et al. Echocardiographic features in patients with critical COVID-19 requiring endotracheal intubation. *Shock*. 2020;14(2):343-346.
17. Brown SM, Pittman J, Miller Iii RR, et al. Right and left heart failure in severe H1N1 influenza A infection. *Eur Respir J*, 2011;37(1):112-118.
18. Cosyns B, Lochy S, Luchian ML, et al. The role of cardiovascular imaging for myocardial injury in hospitalized COVID-19 patients. *Eur Heart J Cardiovasc Imaging*. 2020;21(7):709-714.
19. Fagnoul D, Pasquier P, Bodson L, Ortiz JA, Vincent JL, De Backer D. Myocardial dysfunction during H1N1 influenza infection. *J Crit Care*. 2013;28(4):321-327.
20. Vieillard-Baron A. Is right ventricular function the one that matters in ARDS patients? Definitely yes. *Intensive Care Med*. 2012;35(1):397-399.
21. Wadia SK, Shah TG, Hedstrom G, Kovach JA, Tandon R. Early detection of right ventricular dysfunction using transthoracic echocardiography in ARDS: a more objective approach. *Echocardiography*. 2016;33(12):1874-1879.
22. Peng QY, Wang XT, Zhang LN; Chinese Critical Care Ultrasound Study Group (CCUSG). Using echocardiography to guide the treatment of novel coronavirus pneumonia. *Crit Care*. 2020;24(1):143.
23. Milligan GP, Alam A, Guerrero-Miranda C. Recognizing right ventricular dysfunction in coronavirus disease-2019–related respiratory illness. *J Card Fail*. 2020;26(6):476.
24. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K, et al. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. *Br J Haematol*. 2020;189(5):846-847.
25. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med*. 2020;8(6):e46-e47.
26. Tee A, Wong A, Yusuf GT, Rao D, Sidhu PS. Contrast-enhanced ultrasound (CEUS) of the lung reveals multiple areas of microthrombi in a COVID-19 patient. *Intensive Care Med*. 2020;46(8):1666.
27. Park SJ, Park JH, Lee HS, et al. Impaired RV global longitudinal strain is associated with poor long-term clinical outcomes in patients with acute inferior STEMI. *JACC Cardiovasc Imaging*. 2015;8(2):161-169.
28. Houard L, Benaets MB, de Meester de Ravenstein C, et al. Additional prognostic value of 2D right ventricular speckle-tracking strain for prediction of survival in heart failure and reduced ejection fraction: a comparative study with cardiac magnetic resonance. *JACC Cardiovasc Imaging*, 2019;12(12):2373-2385.
29. Orde SR, Pulido JN, Masaki M, et al. Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. *Crit Care*. 2014;18(4):R149.