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Original Article

Utility of the Right Ventricular Early Inflow-Out Flow Index in the Assessment of Mortality in COVID-19

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) outbreak continues to spread worldwide, hence the increasing attention to the predictors of mortality. However, there is no easy prognostic risk score to predict in-hospital mortality.

We aimed to assess the efficacy of the right ventricular early inflow-outflow index (RVEIO) as a predictor of early mortality in patients with thromboembolism. Additionally, we assessed acute respiratory distress syndrome, which is deemed a complication of COVID-19 and an etiology of acute cor pulmonale.

Methods: This single-center, observational cross-sectional study assessed laboratory data and electrocardiographic and echocardiographic findings of patients with a diagnosis of COVID-19 based on a positive polymerase chain reaction test and lung involvement exceeding 20% in the non-intensive care units of our hospital.

Results: The study population comprised 360 patients (mean age=54.46 y, 61.1% male). The mean RVEIO index was 3.40 ± 1.14, the mean right ventricular peak systolic myocardial velocity (RVsm) was 12.29 ± 3.81 cm/s, and the mean tricuspid annular plane systolic excursion (TAPSE) was 22.41 ± 4.97 cm. No significant difference was found in the RVEIO index between the patients who were discharged and those who expired (3.26 ± 1.25 vs 3.31 ± 1.29, respectively), nor was there a correlation between the RVEIO index and admission to the intensive care unit. The RVEIO index was not a predictor of RV dysfunction, as assessed by RVsm and TAPSE. Patients who suffered from myocardial infarction had a significantly higher RVEIO index.

Conclusions: None of the echocardiographic findings, including the RVEIO index, was an accurate predictor of RV dysfunction, mortality, and inflammation levels in our patients with COVID-19. Accordingly, they should not be relied upon for clinical decision-making and management. ***(Iranian Heart Journal 2021; 22(3): 104-114)***

KEYWORDS: COVID-19, Early inflow-outflow index, Right ventricle, Prognosis, Mortality

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Coronavirus disease 2019 (COVID-19) had affected over 110 million people, with more than 2/4 million deaths the world over, by February 18, 2021. [8] According to official statistics in our country, Iran, the crude mortality ratio (the number of reported deaths divided by the number of total reported cases) is about 5.7%.

Most patients are either asymptomatic or mildly symptomatic, and they recover from the disease with no special treatment. Nonetheless, the disease can be lethal to some patients. Children and younger adults generally suffer from minor disease, while older individuals or those with a history of diabetes mellitus and/or hypertension, cardiac disease, and respiratory disease are susceptible to more severe disease. [1, 2, 3] Patients' demographic-based data are insufficient for the estimation and prediction of the mortality rate, and a remarkable number of patients with none of these predictors eventually die. In other words, other indices are required for the reliable estimation of the severity of the infection and the accurate prediction of mortality among patients with laboratory-confirmed COVID-19 infection.

Several risk scores have been drawn upon in the clinical setting for the risk assessment of COVID-19. [4-7] Nevertheless, the existing literature lacks a single simple assessment to predict mortality. A retrospective study showed an association between right ventricular (RV) dilation measured by echocardiography and in-hospital mortality among patients with COVID-19. [9] Research is ongoing to find other simple echocardiographic methods for risk assessment. Acar et al [10] suggested the echocardiographic right ventricular early inflow-outflow (RVEIO) index as a predictor of RV dysfunction in acute pulmonary thromboembolism.

The pulmonary damage of the coronavirus can be considered an acute lung injury; we, therefore, sought to assess the validity of the RVEIO index for the prediction of mortality in patients with COVID-19.

METHODS

The present study evaluated all patients admitted to the non-intensive care unit (non-ICU) of Dr Shariati Hospital, Tehran, Iran, with a positive reverse transcription-polymerase chain reaction (RT-PCR) test and more than 20% lung involvement in spiral lung computed tomography (CT) scanning during a 4-month period. Patients with documented deep vein thrombosis or pulmonary thromboembolism and poor-quality images were excluded from the study. Ultimately, 360 patients were considered eligible and were enrolled in the study through the census method.

Examinations were prospectively performed using the 5-1 transducer of the SonoSite M-Turbo portable ultrasound system. Left atrial, anteroposterior, and left ventricular (LV) end-diastolic and end-systolic dimensions were measured from the parasternal long-axis view. The size of the RV and the right atrium was measured in the 4-chamber view based on the 2015 American and European guideline. [11] The LV systolic function was assessed via the Simpson method, and the RV systolic function was assessed by a combination of the tricuspid annular plane systolic excursion (TAPSE) and the right ventricular peak systolic myocardial velocity (RVsm) in the 4-chamber view. The diastolic function of the LV was assessed by the measurement of the LV inflow pulsed-wave Doppler at the tip of the mitral valve, and tissue Doppler was applied on the lateral mitral annulus to measure the E' velocity. The E/E' value was calculated by dividing the E velocity of the mitral valve inflow by the E' velocity of the lateral mitral valve annulus.

The RVEIO index was measured with a 2-4 mm sample volume at the tip of the tricuspid

valve leaflets parallel to the RV inflow. The E velocity was obtained in a single breath-hold at end-expiration. The velocity-time integral of the right ventricular outflow tract (RVOT VTI) was measured by tracing the entire envelope recorded at the RVOT in the parasternal short-axis view. The RVEIO index was obtained via the following formula:

RVEIO=E velocity /RVOT VTI

Electrocardiography (ECG) was taken and analyzed from all the patients on the first day. Additionally, a blood test was taken on the first day to check the complete blood count with differentials (CBC diff), the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), troponin I (TnI), and D-dimer.

The patients were followed up during the hospital course for any complications, ICU admission, and mortality.

Statistical Analysis

The study protocol was approved by the Ethics Committee of the Research Department of Tehran University of Medical Sciences. Nominal data were expressed as proportions (%), while continuous data were presented as the mean ± the standard deviation (SD) or the median, as appropriate. The unpaired *t* test or the one-way analysis of variance (ANOVA) was employed to compare the mean values for the distributed continuous variables. The normality of the variables was tested using the Kolmogorov–Smirnov test. Correlation analyses were performed utilizing linear regression models, and the results were expressed as the Pearson correlation coefficients. A *P*-value of less than 0.05 was considered significant. The statistical analyses were performed using SPSS, version 22.0, (SPSS, Inc, Chicago, IL).

RESULTS

The present prospective study was conducted on 360 patients, aged between 18 and 81 years, with a definitive diagnosis of COVID-19. The study population comprised 220 men (61.1%, mean age =61.92 ± 14.42 y) and 140 women (38.9%, mean age =56.69 ± 15.55 y). All the patients had a positive RT-PCR test for the coronavirus and had more than 20% lung involvement in the spiral CT scan.

A history of hypertension and diabetes mellitus was reported in 156 (43.3%) and 108 (30%) patients, correspondingly. Four patients had heart valve prostheses, 28 had a history of coronary artery bypass grafting (CABG), 36 were known cases of LV dysfunction, 18 had chronic obstructive lung disease, 44 had chronic kidney disease, 6 had a history of kidney transplantation, 15 had a history of malignancy, and 7 had current chemotherapy.

The study population's demographic data are summarized in Table 1.

Table 1. Demographic data of the study population

	Number (n)	*P*-value
Age, y (N=360)	< 50 (n=96)	0.000*
	50-70 (n=196)	
	>70 (n=68)	
Sex	Male (n=220)	0.000*
	Female (n=140)	
Past Medical History	Number of Cases	Percentage (%)
DM	108	30
HTN	156	43.3
DLP	20	5.5
PCI	30	8.3
CABG	28	7.7
Prosthetic valve	4	1.1
Malignancy	15	5.5
Chemotherapy	7	1.9
COPD	18	6.6
CRF	44	12.2
Kidney transplantation	6	1.6
Autoimmune disorder	8	2.2
Corticosteroid**	36	10

DM, Diabetes mellitus; HTN, Hypertension; DLP, Dyslipidemia; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; COPD, Chronic obstructive pulmonary disease; CRF, Chronic renal failure

* *P* <0.05, **Corticosteroid before hospitalization

The most frequent presenting symptoms were dyspnea (69.2%) and cough (48.1%). Other symptoms such as headache, diarrhea, myalgia, and abdominal pain were less frequent. About 12.2% of the study population presented with chest pain, and they were ultimately diagnosed with myocardial infarction (MI). In addition, 72.7% of the patients were diagnosed with ST-elevation on ECG. Approximately, 5.9% of the patients with COVID-19 were totally asymptomatic and were discovered incidentally.

The patients had varied clinical courses. Ten out of the 360 patients suffered a cerebrovascular accident while hospitalized, and 4 patients developed myocarditis. No documented deep vein thrombosis and pulmonary thromboembolism were found in all the hospitalized patients with COVID-19. The rate of mortality was 16.6% in patients aged less than 50 years, 24.4% in those aged between 50 and 70 years, and 17.6% in those aged above 75 years (P =0.085). Mortality was not dependent on any previous medical problems such as diabetes mellitus, hypertension, immune deficiency, and chronic renal failure, as well as procedures such as CABG and percutaneous coronary intervention. Interestingly, patients suffering from chronic obstructive pulmonary disease had a mortality rate similar to that in all the other patients. Previous administration of corticosteroids failed to influence the rate of mortality (P =0.127). The relationships between previous medical histories and mortality and complications are summarized in Table 2. (The results are shown as P-values.)

All the patients who suffered a septic shock and those who were intubated had a mortality rate of 100%. Hypertension was the only cardiovascular risk factor correlated with deterioration in the clinical course and the need for ICU admission. Patients with a history of cancer and those with a current chemotherapy regimen were intubated more frequently, suffered septic shocks more commonly, and had a significantly higher mortality rate. Patients with a history of CABG and those with autoimmune disorders had longer ICU stays.

The laboratory data and their correlations with mortality and complications are summarized in Table 3.

Table 2. Relationships between previous medical histories and mortality and complications

	Mortality (n =76)	Discharge (n =284)	ICU Admission (n =144)	ICU Duration <7 d (n =76) 7-14 d (n =68)	Shock (n =76)	MI (n =44)	Myocarditis (n =4)	CVA (n =10)	Intubation (n =284)
DM	0.215	0.215	0.72	0.251	0.250	0.425	0.367	0.364	0.145
HTN	0.132	0.132	0.037*	0.55	0.122	0.791	0.501	0.547	0.78
DLP	0.323	0.323	0.203	0.000*	0.318	0.678	0.838	0.854	0.293
Prosthetic valve	0.078	0.078	0.171	0.311	0.080	0.813	0.907	0.917	0.098
CABG	0.250	0.250	0.138	0.000*	0.245	0.629	0.812	0.831	0.211
COPD	0.697	0.697	0.975	0.799	0.339	0.987	0.629	0.812	0.831
Kidney transplantation	0.074	0.074	0.178	0.310	0.707	0.803	0.902	0.912	0.096
CKD	0.736	0.736	0.743	0.331	0.718	0.423	0.693	0.619	0.614
PCI	0.654	0.654	0.342	0.065	0.641	0.548	0.767	0.791	0.570
Malignancy	0.015*	0.015	0.024*	0.083	0.016*	0.629	0.812	0.831	0.025*
Chemotherapy	0.011*	0.011	0.049*	0.166	0.012*	0.736	0.868	0.882	0.017*
Autoimmune disorder	0.423	0.423	0.303	0.000*	0.419	0.736	0.868	0.882	0.394

ICU, Intensive care unit; MI, Myocardial infarction; CVA, Cerebrovascular accident; DM, Diabetes mellitus; HTN, Hypertension; DLP, Dyslipidemia; CABG, Coronary artery bypass grafting; COPD, Chronic obstructive pulmonary disease; CKD, Chronic kidney disease; CRF, Chronic renal failure; PCI, Percutaneous coronary intervention
* *P* <0.05
Data are shown as *P*-values.

Table 3. Laboratory data and their correlations with mortality and complications

	Mortality (n =76)	Discharge (n =284)	ICU Admission (n =144)	ICU Duration < 7 d (n =76) 7–14 d (n =68)	Shock (n =76)	MI (n =44)	Myocarditis (n =4)	CVA (n =10)	Intubation (n =84)
WBC count	0.924	0.924	0432	0.564	0.822	0.051	0.982	0.523	0.723
Neutrophil, %	0.011*	0.011	0.471	0.041*	0.236	0.054	0.329	0.753	0.023*
Lymphocyte, %	0.234	0.234	0.432	0.024*	0.017*	0.058	0.296	0.771	0.285
Hb	0.231	0.231	0.393	0.936	0323	0.469	0.462	0.000*	0.314
HCT	0.245	0.245	0.293	0.270	0.212	0.579	0.279	0.000*	0.706
Platelet count	0.606	0.606	0.951	0.686	0.697	0.723	0.507	0.000*	0.223
ESR	0.605	0.605	0.342	0.634	0.588	0.841	0.824	0.543	0.650
CRP	0.695	0.695	0.775	0.971	0.694	0.758	0.493	0.999	0.723
BNP	0.884	0.884	0.638	0.000*	0.884	0.884	0.000*	0.000*	0.567
D-dimer	0.480	0.480	0.346	0.667	0.480	0.604	0.000*	0.000*	0.345
TnI	0.236	0.236	0.617	0.495	0.248	0.003*	0.000*	0.779	0.234

ICU, Intensive care unit; MI, Myocardial infarction; CVA, Cerebrovascular accident; WBC, White blood cell; Hb, Hemoglobin; HCT, Hematocrit; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; BNP, Brain natriuretic peptide; TnI, Troponin I
* *P* <0.05
Data are shown as *P*-values.

Table 4. Echocardiographic and electrocardiography data and their correlations with mortality

	Mortality (n =76)	CVA (n =10)	ICU Admission (n =144)	ICU Duration <7 d (n =76) 7-14 d (n =68)	Shock (n =76)	Intubation (n =84)	Discharge (n =284)	Myocarditis (n =4)	MI STEMI (n =33) NSTEMI (n =11)
Heart rate, beat/min <60 (n=40) 60-100 (n=272) >100 (n=48)	0.326	0.812	0.541	0.322	0.334	0.422	0.326	0.011*	0.727
ST-T change ST-depression (n=7) ST-elevation (n=33) T-inversion (n=3)	0.654	0.234	0.605	0.000*	0.732	0.656	0.654	0.000*	0.031*
Arrhythmia AF (n=20) VT (n=36) PAC (n=26)	0.323	0.001*	0.373	0.114	0.373	0.373	0.323	0.856	0.856
QT-interval prolongation, ms (n=22)	0.369	0.877	0.641	0.310	0.378	0.433	0.369	0.000*	0.727
LV dysfunction	0.234	0.828	0.732	0.627	0.418	0.489	0.234	0.794	0.000*
RWMA	0.604	0.000*	0.576	0.534	0.576	0.604	0.604	0.000*	0.000*
Grade of DD	0.567	0.970	0.635	0.593	0.571	0.579	0.567	0.966	0.931
RV dysfunction	0.425	0.526	0.545	0.118	0.142	0.962	0.145	0.479	0.721
Left atrial size	0.445	0.463	0.174	0.939	0.482	0.244	0.445	0.712	0.971
Prosthetic valve	0.624	0.000*	0.724	0.910	0.744	0.624	0.624	0.527	0.527
Pulmonary HTN	0.560	0.703	0.104	0.863	0.456	0.071	0.560	0.670	0.590
RVEIO	0.714	0.481	0.652	0.214	0.674	0.893	0.714	0.957	0.001*

CVA, Cerebrovascular accident; ICU, Intensive care unit; MI, Myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; AF, Atrial fibrillation; VT, Ventricular tachycardia; PAC, Premature atrial contraction; RWMA, Regional wall motion abnormality; DD, Diastolic dysfunction; RV, Right ventricle; HTN, Hypertension; RVEIO, Right ventricular early inflow-outflow index
* *P* <0.05
Data are shown as *P*-values.

The total white blood cell count had no significant correlation with mortality and complications, whereas leukocytosis with a left shift was positively correlated with the total mortality rate and the need for invasive ventilation. Leukopenia was also a predictor of septic shock and longer ICU lengths of stay. Higher ESR and CRP levels were not predictors of death and complications. The level of D-dimer was higher in patients who had cerebrovascular accidents and myocarditis. A higher BNP level was a predictor of a longer ICU length of stay.

Echocardiographic and ECG data and their correlations with mortality are summarized in Table 4.

No ECG changes could predict mortality and ICU admission and duration. None of the echocardiographic findings was significantly correlated with mortality, ICU admission, and ICU length of stay. The RVEIO index could predict neither mortality nor complications, except for patients with MI, who had a higher RVEIO index (*P* =0.001).

DISCUSSION

Angiotensin-converting enzyme 2 (ACE2), a member of the renin-angiotensin system (RAS), is a receptor for the coronavirus and plays a role in its inflammatory pathogenesis. [12, 13] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the host cells of various human organs, including the lung cells, via ACE2 receptors and, besides the direct viral effect, leads to inflammatory and virus-associated immune responses. [14] The degree of lung injury is variable among patients. A retrospective investigation showed that about half of the discharged patients under study had residual abnormalities in chest CT scans. [15] Even in early convalescence, approximately three-quarters of the patients in another study exhibited pulmonary function abnormalities, which resulted in FEV1/FVC [16] and impaired diffusing capacity of the lungs for carbon monoxide (DLCO). [17]

Myocardial Involvement

Puntmann et al [18] showed cardiac involvement in about 78% of recently recovered individuals from the coronavirus by cardiac magnetic resonance imaging, which was independent of severity and even the clinical course of acute illness. The RV is especially “in the eye of the storm” and is placed at a higher risk of failure. [11] The following mechanisms are proposed for RV dysfunction in patients with COVID-19: a higher risk of pulmonary thromboembolism, increased afterload secondary to lung damage, acute respiratory distress syndrome, the negative impact of inflammatory cytokines, and direct ACE2-mediated cardiac injuries. [19] Matteo et al [20] assessed the prognostic value of pulmonary hypertension and RV dysfunction in hospitalized non-ICU patients with COVID-19 and found that pulmonary hypertension rather than RV dysfunction was associated with a worse clinical outcome. Some cohort studies have found contrary results in patients with pulmonary hypertension. According to their findings, the clinical outcome of these patients is benevolent. The authors have proposed several mechanisms for this favorable outcome such as previous use of anticoagulation and pulmonary hypertension-specific medications; impaired pulmonary vasoconstriction, which could hamper perfusion in the non-ventilated areas of the lung; reduced viral entrance due to

a decline in ACE2 expression in pulmonary arterial hypertension; and adaptive lung immune system due to chronic inflammation. [21, 22] Multiple studies have confirmed the increase in morbidity and mortality among patients with preexisting cardiac conditions or risk factors. [23, 24]

In our study, neither RV dysfunction nor pulmonary hypertension led to increased mortality, the need for intubation, or ICU admission. Moreover, none of our patients with a history of cardiac valve replacement, CABG, diabetes mellitus, or hypertension had a significantly worse prognosis than those without risk factors or preexisting cardiac conditions. Only 4 out of our 360 patients developed clinical and imaging signs of active myocarditis.

Although there is a case report of confirmed myopericarditis secondary to the coronavirus, [25] direct cardiac involvement has been difficult to confirm. [26] Linder et al [27] performed histopathologic evaluations of patients who died from COVID-19 and found the evidence of viral existence in the heart with active viral replication and suggested that the most frequent site of the localization of the virus was in interstitial cells or macrophages rather than myocytes themselves.

ECG Analysis

Our ECG analysis yielded no helpful findings for the prediction of mortality. The literature contains reports of a variety of arrhythmias, which are most probably due to myocardial inflammation and the resultant electrophysiological and structural remodeling, [28] with atrial fibrillation being the most common. [29] Sinus bradycardia and inappropriate sinus bradycardia are common findings. They might be the effect of some medications or the inhibitory effects of the virus on the sinus node activity. They are, however, not clinically prognostic. [30] Other arrhythmias such as atrial fibrillation and sinus arrest may happen, although they are likely the consequence of systemic illnesses rather than the effect of the virus on the heart. [31]

Laboratory Data

Our laboratory data showed that patients with a higher neutrophil count and a lower lymphocyte count had more severe disease, were more likely to be admitted to the ICU, and had a higher rate of death. Zhao et al [32] found contrary results in their retrospectively collected data in Wuhan, China, and reported that patients with increased leukocyte counts had higher levels of inflammatory response documented by higher levels of interleukin 6 and CRP. The prognostic value of CRP has been reported in other articles. [33, 34] Be that as it may, in our collective data, elevated first-day CRP and ESR levels did not lead to critical disease. The response to treatment and the descending trend might be more important than the first-day level.

Echocardiographic Findings

Patients hospitalized due to COVID-19 may develop acute cardiovascular syndrome with such different clinical manifestations as cardiomyopathy, acute cardiovascular syndrome, ventricular arrhythmias, and LV and RV dysfunction. The proposed mechanisms are myocarditis, microvascular injury, and stress- or cytokine-related injuries. [35]

We encountered 8 patients with the clinical and ECG presentation of ST-segment-elevation myocardial infarction (STEMI) who had significant epicardial coronary stenosis and 3 patients with troponin release alone who did not have a clinical diagnosis of MI and had normal echocardiography (non-STEMI). Only 1 patient had a globally reduced ejection fraction, and we assumed the case to be acute myocarditis, although it was not documented by pathology.

Elevations in TnI levels in COVID-19 are multifactorial and are mostly due to myocardial injury with no coronary thrombosis in echocardiography. [35]
While a retrospective meta-analysis from China concluded that elevated troponin levels could lead to worse outcomes, we found no such association. [36]
Venous thromboembolism is another common vascular complication of COVID-19, and it can occur in up to 45% of hospitalized patients even despite prophylactic drugs. [37] Still, we found no documented venous thromboembolism in our patients, which may have been because of the routine use of effective anticoagulation or underdiagnosis.
RV enlargement is another multifactorial finding in patients suffering from COVID-19 with an uncertain association with mortality.

The RVEIO Index

The RVEIO index is a simple Doppler echocardiographic measurement calculated by dividing the inflow E-wave velocity of the ventricular chamber by the RVOT VTI. This index is regarded as an ideal index for the diagnosis of severe mitral regurgitation [38, 39] and severe tricuspid regurgitation. [40] Acar et al [10] presented the RVEIO index as a predictor of RV dysfunction, a higher simplified pulmonary embolism severity index, and short-term mortality in acute pulmonary thromboembolism. Our results did not confirm the reliability of this index as a predictor in patients with COVID-19. We found no statistically significant correlations between the RVEIO index and the magnitude of RV dysfunction, the severity of pulmonary hypertension, and the markers of inflammation (ie, ESR and CRP).

CONCLUSIONS

The RVEIO index is not a useful and accurate predictor of RV dysfunction, pulmonary hypertension, mortality, and inflammation levels in patients with COVID-19. Consequently, this index should not be used for clinical decision-making and management. Further prospective studies are mandated to demonstrate the benefits of all echocardiographic parameters for the prediction of mortality in patients suffering from COVID-19.

Conflict of Interest: None declared.

REFERENCES

1. Wenjie Tian, Wanlin Jiang MBBS, , Jie Yao MS, Christopher J. Nicholson, Rebecca H. Li, Haakon H. Sigurslid Luke Wooster, Jerome I. Rotter, Xiuqing Guo. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. J Med Virol. 2020; 92:1875–1883.

2. Fei Zhou, Ting Yu, Ronghui Du, Guohui Fan, Ying Liu, Zhibo Liu, Jie Xiang, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao .Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.Lancet, ISSN: 0140-6736, Vol: 395, Issue: 10229, Page: 1054-1062

3. Chen, T. et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020, 368. https://doi.org/10.1136/bmj.m1091(2019).

4. Duca, A., Piva, S., Focà, E., Latronico, N. & Rizzi, M. Calculated decisions: brescia-COVID respiratory severity scale (BCRSS)/algorithm. Emerg. Med. Pr. 22(5 Suppl), 1–2 (2020).

5. Vincent, J. L. et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care

Med. 22(7), 707–710 (1996). CAS Article Google Scholar

6. Iba, T., Di Nisio, M., Levy, J. H., Kitamura, N. & Thachil, J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. BMJ Open. 7,9. https://doi.org/10.1136/bmjopen-2017-017046(2017).

7. Gue, Y.X., Tennyson, M., Gao, J. et al. Development of a novel risk score to predict mortality in patients admitted to hospital with COVID-19. Sci Rep 10, 21379 (2020). https://doi.org/10.1038/s41598-020-78505-w

8. Johns Hopkins University, 2021. Johns Hopkins Coronavirus Resource Center. Available at. https://coronavirus.jhu.edu/. Accessed on Februrary 18th 2021.

9. Edgar Argulian, Karan Sud, Birgit Vogel, Chandrashekar Bohra, Vaani P. Garg, Soheila Talebi, Stamatios Lerakis, Jagat Narula. Right Ventricular Dilation in Hospitalized Patients With COVID-19 Infection. J Am Coll Cardiol Img. 2020 Jul 15. Epublished DOI:10.1016/j.jcmg.2020.05.010

10. Acar, E, İzci, S, Inanir, M, Yılmaz, MF, Izgi, IA, Kirma, C. Right Ventricular Early Inflow-Outflow Index—A new method for echocardiographic evaluation of right ventricle dysfunction in acute pulmonary embolism. Echocardiography. 2020; 37: 223–230. doi.org/10.1111/echo.14591.

11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015 Jan; 28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003. PMID: 25559473.

12. Jia H. Pulmonary Angiotensin-Converting Enzyme 2 (ACE2) and Inflammatory Lung Disease. Shock. 2016 Sep; 46(3):239-48. doi: 10.1097/SHK.0000000000000633. PMID: 27082314.

13. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G, Wang W. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov. 2020; 6():11.

14. Wentao Ni, Xiuwen Yang, Deqing Yang, Jing Bao, Ran Li, Yongjiu Xiao, Chang Hou, Haibin Wang, Jie Liu, Donghong Yang, Yu Xu, Zhaolong Cao, Zhancheng Gao. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care 24, 422 (2020). https://doi.org/10.1186/s13054-020-03120-0

15. Li K, Fang Y, Li W, Pan C, Qin P, Zhong Y, Liu X, Huang M, Liao Y, Li S. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol. 2020.

16. Huang, Y., Tan, C., Wu, J. et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res 21, 163 (2020). https://doi.org/10.1186/s12931-020-01429-6

17. Su MC, Hsieh YT, Wang YH, Lin AS, Chung YH, Lin MC. Exercise capacity and pulmonary function in hospital workers recovered from severe acute respiratory syndrome. Respiration. 2007; 74(5):511–6.

18. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. Published online July 27, 2020. doi:10.1001/jamacardio.2020.3557

19. John F. Park, Somanshu Banerjee and Soban Umar. In the eye of the storm: the right ventricle in COVID-19 Pulm Circ. 2020 Jul-Sep; 10(3): 2045894020936660. doi: 10.1177/2045894020936660

20. Pagnesi M, Baldetti L, Beneduce A, et al. Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. Heart 2020; 106:1324-1331.

21. Teresa Segura de la Cal, Jorge Nuche, Carmen Jiménez López-Guarch, Carmen Pérez-Olivares, Maite Velázquez, Francisco López-Medrano, María Jesús López Gude, Sergio Alonso Charterina, Fernando Arribas Ynsaurriaga, Pilar Escribano Subías. Unexpected Favourable Course of Coronavirus Disease 2019 in Chronic Thromboembolic Pulmonary Hypertension Patients.Archivos DE Broncoeumologica. DOI: 10.1016/j.arbres.2020.06.004

22. Jorge Nuche, Carmen Pérez-Olivares, Teresa Segura de la Cal, Carmen Jiménez López-Guarch, Fernando Arribas Ynsaurriaga, Pilar Escribano Subías. Clinical course of COVID-19 in pulmonary arterial hypertension patients.Revista Espanola de Cardiologica. 2020; 73(9):775-778. DOI: 10.1016/j.rec.2020.05.015.

23. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1017

24. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

25. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1096

26. Yancy CW, Fonarow GC. Coronavirus Disease 2019 (COVID-19) and the Heart—Is Heart Failure the Next Chapter? JAMA Cardiol. Published online July 27, 2020. doi:10.1001/jamacardio.2020.3575

27. Lindner D, Fitzek A, Bräuninger H, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol. Published online July 27, 2020. doi:10.1001/jamacardio.2020.3551

28. Babapoor-Farrokhran S, Rasekhi RT, Gill D, Babapoor S, Amanullah A. Arrhythmia in COVID-19 [published online ahead of print, 2020 Aug 14]. SN Compr Clin Med. 2020; 1-6. doi:10.1007/s42399-020-00454-2

29. Gopinathannair R, Merchant FM, Lakkireddy DR, Etheridge SP, Feigofsky S, Han JK, Kabra R, Natale A, Poe S, Saha SA, Russo AM COVID-19 and cardiac arrhythmias: a global perspective on arrhythmia characteristics and management strategies.J Interv Card Electrophysiol. 2020 Nov; 59(2):329-336

30. Capoferri G, Osthoff M, Egli A, Stoeckle M, Bassetti S. Relative bradycardia in patients with COVID-19 [published online ahead of print, 2020 Aug 18]. Clin Microbiol Infect. 2020;S1198-743X(20)30495-X. doi:10.1016/j.cmi.2020.08.013

31. Anjali Bhatla, Michael M. Mayer, Srinath Adusumalli,Matthew C. Hyman, Eric Oh, Ann Tierney, et al. COVID-19 and cardiac arrhythmias. Heart Rhythm, Vol 17, No 9, September 2020 .1439-1443. https://doi.org/10.1016/j.hrthm.2020.06.016.

32. Zhao K, Li R, Wu X, et al. Clinical features in 52 patients with COVID-19 who have increased leukocyte count: a retrospective analysis [published online ahead of print, 2020 Jul 10]. Eur J Clin Microbiol Infect Dis. 2020; 1-9. doi:10.1007/s10096-020-03976-8

33. Sahu BR, Kampa RK, Padhi A, Panda AK. C-reactive protein: A promising biomarker for poor prognosis in COVID-19 infection. Clin Chim Acta. 2020; 509:91-94. doi:10.1016/j.cca.2020.06.013

34. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, Ye L, Xiong J, Jiang Z, Liu Y, Zhang B, Yang W. Prognostic value of C-reactive protein in patients with COVID-19. Clin Infect Dis. 2020 May 23:ciaa641. doi:

10.1093/cid/ciaa641. Epub ahead of print. PMID: 32445579; PMCID: PMC7314209.

35. Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome. Circulation. 2020; 141(23):1903-1914. doi:10.1161/CIRCULATIONAHA.120.047349

36. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis [published online March 10, 2020]. Prog Cardiovasc Dis. doi: 10.1016/j.pcad.2020.03.001.

37. Zhang L, Feng X, Zhang D. et al. Deep vein thrombosis in hospitalized patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: prevalence, risk factors, and outcome. Circulation 2020; 142 (02) 114-128

38. Aika Matsumoto, Toshiaki Mano, Akiko Goda, Shohei Fujiwara, MasatakaSugahara, Kumiko Masai, Yuko Soyama, Tohru Masuyama, significance of left ventricular early inflow-outflow index for mitral regurgitation severity., J Am Coll Cardiol. 2016 Apr, 67 (13 Supplement) 2217.

39. Lee, Ming-Ming, Salahuddin, Ayesha, Garcia, Mario, Spevack, Daniel. Left Ventricular Early Inflow-Outflow Index: A Novel Echocardiographic Indicator of Mitral Regurgitation Severity. May 2015. Journal of the American Heart Association. 4(6):e000781-e000781. DOI: 10.1161/JAHA.113.000781

40. Izgi IA, Acar E, Kilicgedik A, Guler A, Cakmak EO, Demirel M, Izci S, Yilmaz MF, Inanir M, Kirma C. A new and simple method for clarifying the severity of tricuspid regurgitation. Echocardiography. 2017 Mar; 34(3):328-333. doi: 10.1111/echo.13458. Epub 2017 Jan 28. PMID: 28130798.