Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/15111
DOI URL: http://dx.doi.org/10.21474/IJAR01/15111

*RESEARCH ARTICLE*

# EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS OF CARDIOVASCULAR DYSFUNCTION IN CRITICALLY ILL COVID-19 PATIENTS: A PROSPECTIVE COHORT STUDY

**Dr. Ajeetviswanath Thanjavur Prabhakaran[1], Dr. Karthik Ram Ananthakrishnan[1], Dr. Sulagna Bhattacharjee[1], Dr. Kapil Dev Soni[2], Dr. Richa Aggarwal[2], Dr. Deepthi Siddharthan[3] and Dr. Anjan Trikha[1]**

1. Dept. of Anesthesiology, Pain Medicine and Critical Care, AIIMS, New Delhi.
2. Dept. of Critical and Intensive Care, JPNA Trauma Centre, AIIMS, New Delhi.
3. Dept. of Cardiology, AIIMS, New Delhi.

## Manuscript Info

***Manuscript History***
Received: 30 May 2022
Final Accepted: 30 June 2022
Published: July 2022

***Key words:-***
Cardiac Dysfunction, COVID-19, SARS-COV2

## Abstract

**Background:**Early reports indicate that cardiac involvement can commonly occur in COVID-19 patients. This prospective observational study aimed to evaluate myocardial dysfunction in critically ill COVID-19 patients.

**Methods:**Forty adult patients with confirmed COVID-19 disease admitted to the intensive care unit of a tertiary care hospital were included, following which demographic, baseline laboratory and serial echocardiography was done on days 1, 3, 5 & 7 to assess global or regional wall motion abnormality, left ventricular function [ejection fraction (LVEF), E/e') and right ventricular function [tricuspid annular plane excursion (TAPSE), tricuspid regurgitation (TR) jet)]. Any new onset ECG changes were also noted.

**Results:**Patients (n=40) had median (IQR) age of 51.5 (38.5- 63.5) and median (IQR) SOFA score of 5.5 (5- 7). Median (IQR) P/F ratio of the included patients at the time of recruitment was 250 (180- 300) and median (IQR) Charlson's comorbidity index was 2 (1- 4). Proportion (95% CI) of patients died during hospital stay was 15 (7.1- 29.1) %. We found that, on day 1, 25% patients had mild to moderate LV dysfunction. Although LVEF was statistically higher in patients receiving mechanical ventilation, LVEF, E/e', TAPSE and TR jet did not change significantly from base line till day 7, in both mechanically ventilated and nonventilated patients, or in survivors and non-survivors. However, LVEF correlated with $PaO_2/FiO_2$ ratio (P/F) ratio at day 3 (rho= 0.46, p=0.003), 5 (rho= 0.47, p=0.002) and 7 (rho= 0.41, p=0.01), whereas TR jet with correlated inversely wit P/F ratio at day 1 (rho= -0.39, p=0.01) and 3 (rho= -0.39, p=0.01).

**Conclusion:** Our study highlights that although P/F ratio correlated with both left ventricular and right function, the dynamics of both left ventricular and right ventricular function was non- progressive in both mechanically ventilated and as well as spontaneously breathing patients, and similar in both survivors and non survivors.



**Corresponding Author:-Dr. Sulagna Bhattacharjee**
Address:- Assistant Professor, Dept. of Anesthesiology, Pain Medicine and Critical Care All India Institute of Medical Sciences, New Delhi.

## Introduction:-

The third novel coronavirus in 17 years emerged in Wuhan, China, in December 2019 (1). Phylogenetics has indicated that severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) is closely related to bat-derived SARS-like coronaviruses (2). Early reports from Wuhan described the associated coronavirus disease 2019 (COVID-19) as a SARS-like atypical pneumonia in which 26% to 33% of patients required intensive care and 4% to 15% died (1,3,4). A large case series of 72314 infected individuals has since refined these initial estimates in China to severe disease in 14% and a case-fatality rate of 2.3% (5).

The surface spike protein of the coronavirus binds with the human angiotensin converting enzyme (ACE) receptor in the respiratory epithelium to initiate infection. However, expression of ACE receptor is found in heart and intestinal epithelium also (6). Though the commonest presenting symptoms of SARS- CoV-2 infection are fever, cough and shortness of breath, atypical and non-respiratory symptoms are also common. A study from China reported that nearly 23% SARS- CoV-2 infected patients admitted in ICU, had some degree of cardiovascular dysfunction (7). A higher level of cardiac troponin was also found in patients who died from SARS- CoV-2 infection than who survived (8). Though, there is report of serial increase in cardiac troponin level in SARS- CoV-2 infected patients who didn't survive, no study has evaluated serial myocardial function in critically ill SARS- CoV-2 infected patients. In this prospective study, serial myocardial function in adult SARS- CoV-2 infected patients were evaluated over a period of 7 days.

## Methods:-

After obtaining permission from the institute ethics committee and informed consent from their legally acceptable representatives, 40 adult patients (aged between 18 and 75y) of either sex, fulfilling WHO case definition of SARS-CoV-2 infection and admitted in an intensive care unit at AIIMS, New Delhi were included in the study. Patients with known coronary artery diseases, cardiomyopathy and valvular heart diseases were excluded from this study. Demographic and baseline clinical data were collected at the time of ICU admission. Standard intensive care protocol as per current Surviving Sepsis Guidelines and standard low tidal volume ventilation for management of ARDS were followed in all ventilated patients. Protocolized weaning and extubation was followed as per patient parameters. Fluid and vasopressor management were guided by hemodynamic variables and point of care ultrasound. Broad spectrum antibiotics were initiated at presentation as per institute protocol and appropriate cultures sent (blood, urine, abdominal fluid and tracheal aspirate whenever suitable). Bedside transthoracic echocardiography was performed by an intensivist with an experience of having performed at least 50 point of care echocardiography. Left heart assessment included the measurement of ejection fraction by Simpson's biplane method, assessment of any regional wall motion abnormality in the parasternal short axis view (9). It also included the measurement of E/e' ratio using pulse wave and tissue doppler measurements across the mitral valve annulus to detect any underlying diastolic dysfunction (10). Right ventricular function assessment included assessment of any global or regional wall motion abnormality. TAPSE was calculated as the total excursion of the tricuspid annulus measured by M-mode in the echocardiographic apical 4-chamber view. TR jet was calculated using continuous wave Doppler across the tricuspid annulus (11). Any new onset ECG changes (rhythm, bundle branch block, ST-T changes, QT prolongation), were also noted.

### Statistical Analysis

All collected data were entered in a spreadsheet. Continuous data were represented as median and interquartile range (IQR) and categorical data were represented as absolute number and percentages. For comparison of unrelated samples, Mann Whitney U test was performed, and categorical variables were compared by Fisher exact test. For identification of change in echocardiographic variables (LV EF, e/e`, TR jet and TAPSE) over time, repeated measure one-way ANOVA was performed. Effect of mechanical ventilation on the change in echocardiographic variables were identified by two-way repeated measure ANOVA. All statistical analyses were performed in Graph Pad Prism (GraphPad Prism version 8.0.0 for Mac OS, GraphPad Software, San Diego, California USA).

## Results:-

In this prospective study, 40 patients with median (IQR) age of 51.5 (38.5- 63.5) and median (IQR) SOFA score of 5.5 (5- 7) were recruited. Median (IQR) P/F ratio of the included patients at the time of recruitment was 250 (180-300) and median (IQR) Charlson's comorbidity index was 2 (1- 4). Proportion (95% CI) of patients died during hospital stay was 15 (7.1- 29.1) %. Baseline echocardiographic parameters of the patients have been reported in table 1. Amongst all patients, n=12 patients were mechanically ventilated. On day 1, 25% patients (10 of 40) had

some degree of LV dysfunction as per American Society of Echocardiography criteria (12). Baseline laboratory investigations and blood gas data were represented in table 2. LV EF was statistically higher in patients who were mechanically ventilated than who were not [p=0.04, Mann Whitney U test]. Five patients received remdesvir. All patients received hydroxychloroquine (HCQ) and doxycycline as a part of standard institutional protocol. HCQ was withheld in those with prolonged corrected QT interval or with onset of arrhythmias. All other echocardiographic parameters were similar between patients who were mechanically ventilated and not ventilated. Two patients developed new onset atrial fibrillation, one patient developed ST segment depression and another patient developed ventricular premature contractions.

There was no change in the LV EF (p=0.99), E/e` (p=0.99), TAPSE (p=0.48) and TR jet (p=0.91) over time till day 7 from baseline [repeated measure one-way ANOVA]. Two- way repeated measure ANOVA with requirement of mechanical ventilation as an interaction term also revealed that LV EF (p=0.39), E/e` (p=0.92), TAPSE (p=0.28) and TR jet (p=0.86) remained unaltered over time. Figure 1 depicted changes of LV EF, E/e`, TAPSE and TR jet over time in all patients. There was no statistically significant difference in LV EF, E/e`, TAPSE and TR jet at any of the study point between survivors and non- survivors (figure 2).

Statistically significant correlations were found between LV EF and P/F ratio at day 3 (rho= 0.46, p=0.003), day 5 (rho= 0.47, p=0.002) and day 7 (rho= 0.41, p=0.01) but not at day 1 (rho= 0.23, p=0.15). No correlation was found between TAPSE and E/e` with P/F ratio at any time point. Statistically significant negative correlations were found between TR jet and P/F ratio at day 1 (rho= -0.39, p=0.01) and day 3 (rho= -0.39, p=0.01) but not at day 5 (rho= -0.28, p=0.08) and day 7 (rho= -0.27, p=0.09).

## Discussion:-

This prospective observational study in critically ill COVID-19 patients revealed that although LVEF was statistically higher in patients receiving mechanical ventilation, LVEF, E/e', TAPSE and TR jet were similar in both mechanically ventilated and non-ventilated groups, or among survivors and non-survivors, and they did not change significantly over the first week of ICU stay. However, LVEF correlated with P/F ratio at day 3, 5 and 7 whereas TR jet with correlated inversely wit P/F at day 1 and 3.

Myocardial injury or involvement from SARS- CoV-2 infection is common; though the possible mechanisms of myocardial injury are yet to be elucidated. Direct myocardial involvement through the ACE2 receptors and/ or indirect involvement by 'cytokine storm' and hypoxia induced excessive intracellular calcium leading to cardiac myocyte apoptosis the are possible pathways of myocardial involvement in such cases (13, 14). However, presence of 'cytokine storm' in SARS- CoV-2 infected patients has been questioned in recent researches (15).

Incidence of myocardial injury in SARS- CoV-2 infected patients is variable and obviously dependent upon the definition used. In a small series of 41 patients, around 12% patients had myocardial injury defined by elevation of cardiac biomarkers and/ or new onset abnormalities in echocardiography or ECG (1). A series of 138 patients from China also reported that overall incidence of myocardial injury was around 7%, but it was 22% in patients who required intensive care (4). Another study reported higher level of cardiac troponin in non-survivors and cardiac troponin gradually elevated over time in non-survivors (8).

With best of our knowledge, the present study is different from all previously published studies. In our study, cardiovascular function was assessed by bedside echocardiography serially over a period of 7 days from the date of ICU admission along with disease progression as assessed by P/F ratio. Presence of any degree of left ventricular dysfunction was 25% in our study, but LV dysfunction was of mild degree in all except one patient who developed moderate dysfunction. Another interesting finding of our study is that we have found that the dynamics of both left ventricular and right ventricular function was non- progressive in both mechanically ventilated and as well as spontaneously breathing patients. We have also found that all the measured echocardiographic parameters were similar at all study time points in survivors and non- survivors. In our study, LV EF was statistically higher at baseline in patients who were mechanically ventilated which is probably explained by a reduction in afterload with positive pressure ventilation. Hypoxemia is probably associated with some degree of both left and right ventricular dysfunction, evidenced by correlation of both LV EF and TR jet with P/F ratio. This can be explained by the probable mechanism of hypoxemia causing cardiac myocyte apoptosis (13, 14).

**Limitations**

Our study has a few limitations. Echocardiographic assessment was continued till 7 days since ICU admission only and cardiac biomarkers were also not assessed.

## Conclusion:-

Functional left ventricular dysfunction of mild degree is common in SARS- CoV-2 infected patients but clinically significant dysfunction is uncommon. Effect of cardiovascular dysfunction on clinical outcome needs to be elucidated.

**Table 1:-** Baseline clinical, laboratory and blood gas data of all patients.

| | All patients (n=40) | Mechanical ventilation Required (n=12) | Mechanical ventilation not required (n=28) | Significance |
|---|---|---|---|---|
| Age | 51.5 (38.5- 63.5) | 53 (41.5- 66) | 50.5 (38.5- 63.5) | p=0.68 |
| CCI | 2 (1- 4) | 3.5 (2- 5) | 1.5 (0- 3) | p=0.04 |
| Hemoglobin (g/dl) | 11.9 (9.9- 13.3) | 10.7 (8.1- 12.7) | 12 (10.2- 13.6) | p=0.17 |
| Total leucocyte count (cells/cumm$^3$) | 8950 (6035- 12535) | 7750 (5075- 9750) | 10150 (6750- 13485) | p=0.20 |
| Absolute neutrophils cells (cells/cumm$^3$) | 6199 (3680- 9429) | 5467 (3363- 7581) | 7910 (4403- 9693) | p=0.36 |
| Absolute lymphocyte count (cells/cumm$^3$) | 1661 (960- 2241) | 1053 (725- 1890) | 1736 (1224- 2383) | p=0.09 |
| Platelet (per cumm$^3$) | 155500 (93500- 243000) | 153500 (96500- 243500) | 15700 (91000- 24300) | p=0.91 |
| INR | 1.1 (1- 1.2) | 1.1 (1.06- 1.2) | 1.05 (1- 1.1) | p=0.17 |
| Albumin (g/dl) | 2.85 (2.25- 3.45) | 2.8 (2.15- 4.1) | 2.85 (2.45- 3.3) | p=0.88 |
| Creatinine (mg/dl) | 0.8 (0.65- 1.1) | 0.8 (0.65- 1.15) | 0.8 (0.65- 1.05) | p=0.87 |
| Lactate (mmol/L) | 1 (0.9- 1.55) | 1 (0.9- 1.35) | 0.85 (0.95- 1.6) | p=0.99 |
| SOFA Score | 5.5 (5- 7) | 4.5 (3- 5.5) | 2.5 (2- 4) | p=0.06 |
| P/ F ratio | 250 (180- 300) | 225 (120- 285) | 258 (195- 300) | p=0.19 |

**Table 2:-** Cardiac function assessed by echocardiography at baseline.

| | All patients (n=40) | Mechanical ventilation required (n=12) | Mechanical ventilation not required (n=28) | Significance |
|---|---|---|---|---|
| LV EF | 57 (51.5- 60) | 59 (56.5- 61) | 55.5 (50- 58) | p=0.04 |
| E/e` | 7.45 (6.28- 8.6) | 7.5 (5.99- 9.05) | 7.45 (6.4- 7.98) | p=0.98 |
| TAPSE | 1.96 (1.8- 2.2) | 2.09 (1.85- 2.3) | 1.91 (1.8- 2.1) | p=0.15 |
| TR Jet | 1.95 (1.36- 2.28) | 2.02 (1.9- 2.61) | 1.59 (1.3- 2.24) | p=0.11 |
| LV RWMA present | 2 | 0 | 2 | p>0.99 |
| RV RWMA present | 0 | 0 | 0 | NA |

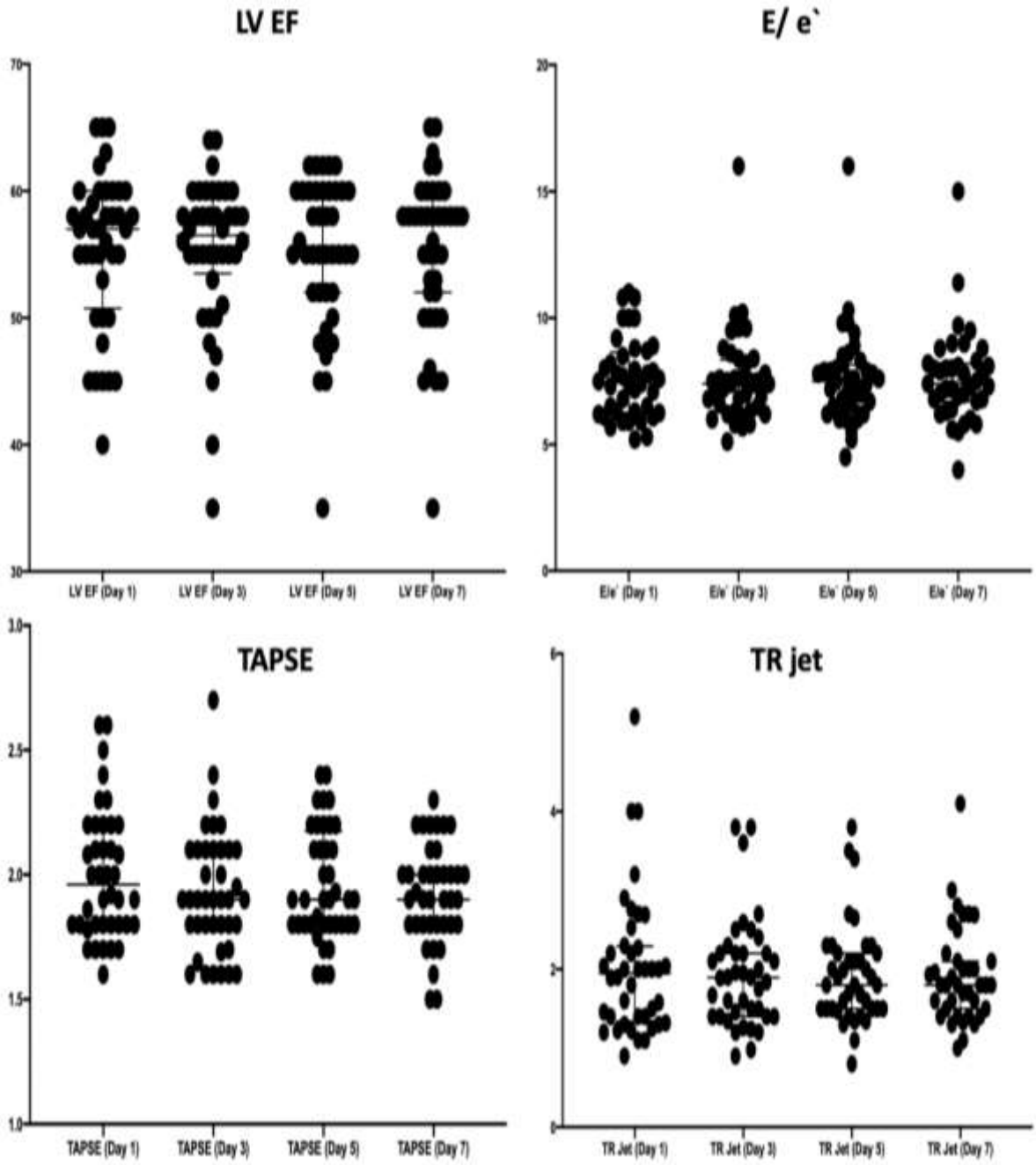


**Figure 1:-** Scatter dot plot showing LV EF, E/e`, TAPSE and TR jet in all patients measured at day 1, day 3, day 5 and day 7.

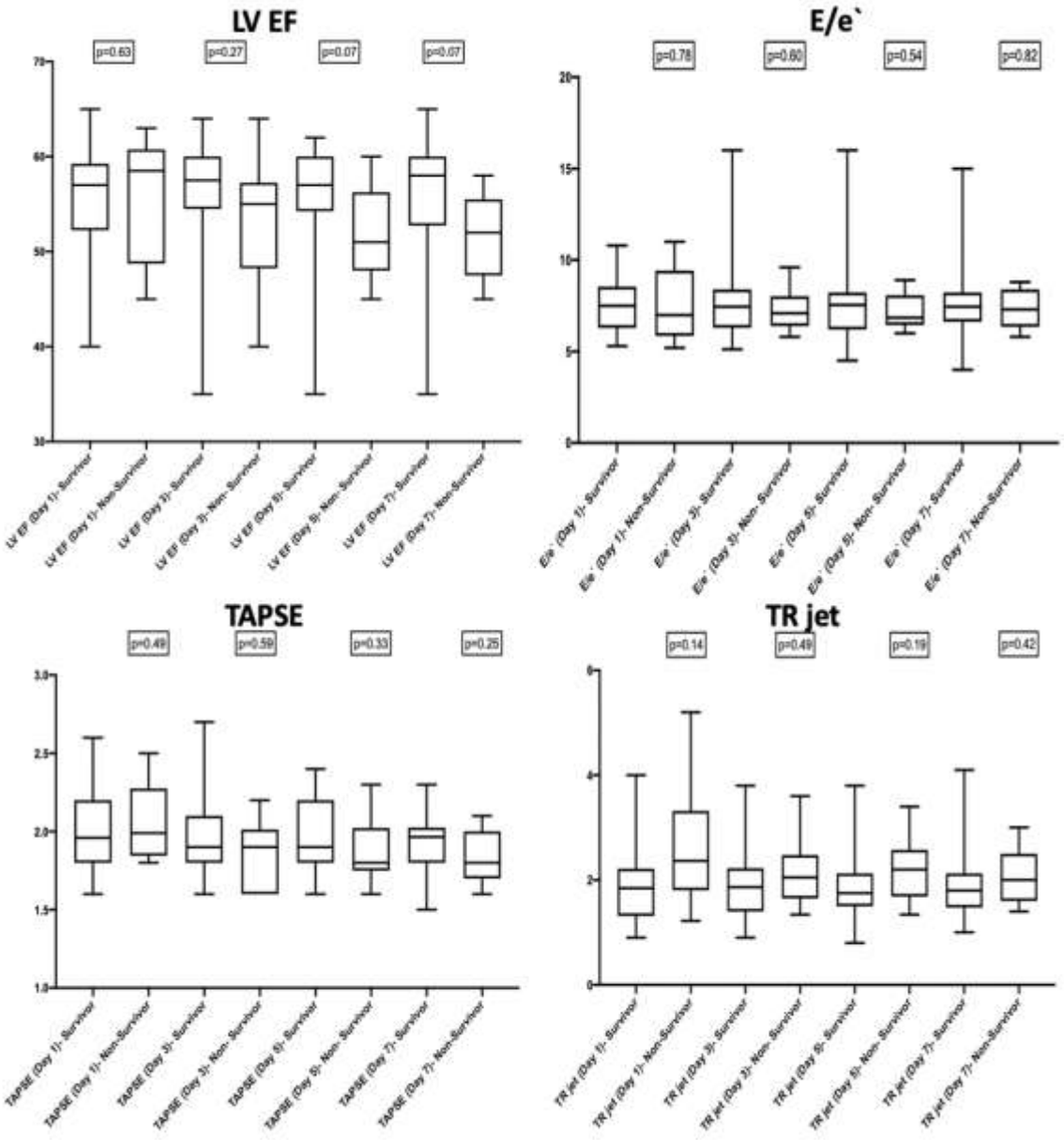


**Figure 2:-** Box- whisker plot showing LV EF, E/e`, TAPSE and TR jet in all patients measured at day 1, day 3, day 5 and day 7 in survivors and non- survivors.

## References:-

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020 Feb 15;395(10223):497–506.
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet. 2020 Feb 22;395(10224):565–74.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727–33.
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061–9.

5. 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. 2020 Apr 7;323(13):1239–42.
6. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res. 2020;126(10):1456-1474.
7. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study [published correction appears in Lancet Respir Med. 2020 Apr;8(4):e26]. Lancet Respir Med. 2020;8(5):475-481.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–1062.
9. Chengode S. Left ventricular global systolic function assessment by echocardiography. Ann Card Anaesth. 2016 Oct;19(Suppl 1):S26–34.
10. Galderisi M. Diagnosis and Management of Left Ventricular Diastolic Dysfunction in the Hypertensive Patient. Am J Hypertens. 2011 May 1;24(5):507–17.
11. Zaidi A, Knight DS, Augustine DX, Harkness A, Oxborough D, Pearce K, et al. Echocardiographic assessment of the right heart in adults: a practical guideline from the British Society of Echocardiography. Echo Res Pract. 2020 Mar 1;7(1):G19–41.
12. Kosaraju A, Goyal A, Grigorova Y, et al. Left Ventricular Ejection Fraction. [Updated 2020 May 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459131/
13. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and Cardiovascular Disease. Circulation. 2020;141(20):1648-1655.
14. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17(5):259-260.
15. Kox M, Waalders NJB, Kooistra EJ, Gerretsen J, Pickkers P. Cytokine Levels in Critically Ill Patients With COVID-19 and Other Conditions. **JAMA.** Published online September 03, 2020. doi:10.1001/jama.2020.17052.