VOLUME - 12, ISSUE - 03, MARCH - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

General Medicine

CLINICAL SPECTRUM OF ACUTE CORONARY SYNDROME IN SARS-COVID-19 AND NON-SARS-COVID-19 PATIENTS - A COMPARATIVE STUDY

Chandhini. S — Junior resident, Department of general medicine Mahatma Gandhi Medical College and Research Institute, Puducherry, India

Mohammed Hanifa — Professor and HOD, Department of general medicine Mahatma Gandhi Medical College and Research Institute, Puducherry, India

ABSTRACT

Background: COVID-19 is caused by virus named Severe acute respiratory syndrome (SARS-nCoV) which can be transmitted between humans via respiratory droplets,initially recognised as respiratory disease with predominate respiratory symptoms, it has been found that it had interaction with and affects the cardiovascular system as it leads acute myocardial infarction (MI), myocarditis simulating a ST elevation MI (STEMI) presentation, non-ischemic cardiomyopathy, coronary spasm, arrhythmias and cardiogenic shock.

KEYWORDS : Acute ST elevation myocardial infarction,SARS COVID-19

INTRODUCTION:

Novel Coronavirus disease (nCOVID-19), declared as pandemic and announced as a Public Health Emergency of International Concern (PHEIC) due to its exponential rise with incessantly rising the casualties worldwide.[1,2] It was manifested as asymptomatic/mild symptoms to severe illness and death, a serious concern in the medical community.[3,4]

Initially ascertained as a respiratory condition with a preponderance of respiratory symptoms , it has now unearthed with the signs of cardiovascular disease .[5,6] The prevalence of CAD ranged from 5% to 16 percentage.[5,7,8] Although a recent study from China, reported that 12% of patients had COVID-19– associated acute cardiac injury, manifesting as an ejection fraction (EF) decline and troponin-I elevation, and the American College of Cardiology (ACC) clinical bulletin has highlighted the cardiac implications of COVID-19 with the association between COVID-19 –associated cardiac injury and its mortality.[9,10] Manifestations include acute myocardial infarction (MI), myocarditis simulating a ST elevation MI (STEMI) presentation, non-ischemic cardiomyopathy, coronary spasm, arrhythmias and cardiogenic shock.[5,6,11] Also numerous pathophysiologic mechanisms were the systemic viral infection may lead to a higher risk of plaque destabilization and acute coronary syndrome (ACS), yet the precise mechanisms are not clearly understood.[5,11]

The clinical spectrum of COVID-19 CAD manifestations was particularly wide as it ranges from asymptomatic to life-threatening or terminal forms with multi-organ involvement and systemic inflammatory response syndrome (SIRS).[12] The ambiguities about the symptoms and the management of these cardiologic emergencies masked by the respiratory symptoms should be understood as the initial symptoms mimics similar to other viral respiratory syndromes.[1]

Thus, a great effort to be impanelled by the healthcare providers to expert the near future short- and long-term complications of COVID-19 with ACS symptoms. Added to that, optimizing the diagnostic and therapeutic resources, and ensuring the maximum protection to these patients by early identification and diagnosis were crucial. Hitherto, the challenge in differentiating the diagnosis between non-COVID ACS and COVID ACS due to restricted availability of diagnostic tools, lack of standardized protocols to balance between the timely management of ACS and COVID-19 with redistribution of healthcare resources and hospital environment might trigger the delay in the treatment of high-risk ACS, with increased long-term complication.[1,4,5,12] Also, patients with COVID-19 symptoms without any CAD might mimic the MI, to be identified earlier. Thus, in the present study we assess the clinical features, electrocardiogram (ECG), echocardiogram (ECHO), cardiac enzymes, in-hospital outcome, morbidity, and mortality of ACS who were presented with COVID and with NON-COVID to make a comparison.

OBJECTIVES

1. To assess and compare the clinical features of acute coronary syndrome in COVID-19 and non-COVID-19 patients.
2. To assess and compare electrocardiography (ECG) changes, cardiac enzymes, echocardiogram (ECHO), morbidity and mortality in Covid-19 and Noncovid-19 patients.

METHODOLOGY

Study Design And Setting:

The present hospital-based prospective comparative study was conducted in the Department of General Medicine in a tertiary care teaching hospital in rural Puducherry, India for the period of 18 months.

Study Population:

Patients presenting with clinical features suggestive of ACS, confirmed by ECG, Cardiac enzymes, and ECHO, and admitted under General medicine were enrolled with the inclusion criteria of age >18 years, both sex, patients with new ECG changes (STEMI/NSTEMI/Unstable angina), elevated cardiac enzymes, and ECHO findings of regional wall motion abnormalities. Patients were categorized into two groups: RT-PCR positive for SARS-COVID19 as group I and RT-PCR was negative as group II. Patients who are, known case of cardiac abnormalities, patients who underwent Coronary artery bypass grafting surgery (CABG), PCI, and other cardiac surgeries, patients on anticoagulants, pregnant females, and participants were excluded from the study.

Sample Size:

Sample size was determined using the sample size calculator android app developed by Mr. Thai Thanh Truc[13] (version_1.0, Sydney, Australia) and calculated to be 200. Considering the proportion in group as 74% and in group to as 5%, in the ratio of 1:4 with 95% as type I error and the power of 80%, the sample size calculated was 200. (Group I – 40; Group II – 160). The formula used to calculate was $p = \frac{p_1 + r p_2}{1+r}$ where $n \geq \frac{[Z_{1-\frac{\alpha}{2}}\sqrt{(r+1)\bar{p}(1-\bar{p})} + Z_{1-\beta}\sqrt{rp_1(1-p_1)+p_2(1-p_2)}]^2}{r(p_2-p_1)^2}$

Sampling Procedure:

Patients with eligibility criteria were selected using systematic random sampling methods into two groups as patients with COVID-19 (Group I) and non-COVID-19 condition (Group II).

Statistical Analysis:

The data was entered in MS EXCEL (Ver_2007) software. Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) (Version 24.0, developed by IBM Corp, Armonk, New York) software. Descriptive statistics were calculated for all categorical variables and measured in terms of frequencies and percentages. Continuous variables which followed normal distribution were calculated and presented as mean and standard deviation (SD) or median with interquartile range (IQR). Data were analyzed based on the type of variables and the normal distribution between two groups. Categorical variables which follow nonparametric distribution were analyzed using Pearson's Chi-square test or two-tailed Fisher's exact test. Independent t-test was used for continuous variables and those followed normal distribution. Ordinal variables were calculated using the Mann-Whitney U test. Statistical significance was considered as a p value of <0.05 for the data analyzed.

Survival analysis with Kaplan-Meier was conducted to compare their median survival time across the arrhythmia status with the assumptions that amount, and pattern of censorship should be same in all group was tested by using scatter plot and chi-square test. Pairwise comparison using Log-rank, Breslow, and Tarone-ware tests, was done to assess the statistical significance. Cox-regression method was used to evaluate the risk factors for the primary outcome effect of COVID on the ACS patients and the secondary outcome with mortality. Statistical significance was considered as a p value of <0.05 for the primary end point.

Ethical Issues:

The study was approved by the Institutional Human Ethics Committee (MGMCRI/Res/01/2020/96/IHEC/358) and followed the principles laid down in the declaration of Helsinki.

RESULT:

The mean age of the study participants with COVID was 64.00 ± 13.58 years, and with non-COVID was 55.64 ± 10.50 years were statistically significant ($p < 0.001$; 95% CI (Confidence Interval): 4.466 – 12.259). The male and female in group I was 31/9 and in group II was 110/50 and not significant. The clinical features and co-morbidity of the patients in both groups were projected in **figure 1.** Laboratory assessments were given in **table 1**.

The outcome of the ACS patients based on the COVID status given in **table 2**. The median length of the hospital stays among ACS patients with both COVID and non-COVID patients were five days (interquartile range (IQR): 5 – 7 days) and found to be non-significant statistically (p 0.189).

Kaplan-Meier survival analysis was conducted to compare their median survival time across the arrhythmia status. Scatter plot showed that the pattern of censored data is similar in groups, but the chi-square results (p 0.002) shows that there is significant difference in the amount of censoring between the two groups (58.8% censored in ACS patients with arrhythmias and 94.5% censoring with no-arrhythmia). **(Table 3, figure 2)** Pairwise comparison using Log-rank, Breslow, and Tarone-ware tests, showed that the median survival time of the ACS patients was found to be statistically significant difference between the patients with arrhythmia and no-arrhythmia. The graph shows that there is difference between the survival rates across the ACS patients with arrhythmia and no arrhythmia which is statistically significant (Log-rank *p* 0.002)

For the assumption of Cox-proportional hazards regression following steps were done. Log minus log curves were done for COVID status, 2D ECHO result, and arrhythmia status showed that the curves are parallel to each other without overlapping. Thus, the proportional hazard assumption met. The standard error value of all the variables like between 0.001 to 5.0, hence no multicollinearity between the variables were found. There is significant reduction in the -2-log likelihood value (126.567) from Block 0 to Block 1, hence the model is fit. (Table 4, figure 3)

A Cox proportional Hazard regression analysis was done to find out the effect of age, gender, COVID status, arrhythmia status, laboratory markers (troponin I, CPK NAC, CPK MB), ECG and 2D ECHO findings in the occurrence of death in ACS patients. After adjusting the other variables hazard ratio was assessed for COVID status, arrhythmia and 2D ECHO. When compared with females, the hazard of occurrence of death is 1.01 times higher in males and it is statistically non-significant. The hazard ratio for COVID-19 positive people for experiencing death is 2.51 times higher when compared to patients with no COVID, yet statistically non-significant. The hazard ratio for occurrence of death in patients with arrhythmia is 4.29 times higher when compared to patients without arrhythmia and it is statistically significant (*p* value 0.006; 95% CI: 1.507 – 12.215). Thus, for each day increase in arrhythmia, the hazard of experiencing death increases by 4.29 times. **(Table 4)** The adjusted survival curve and hazard function for patients with ACS after adjusting for age, gender, ECG, and laboratory parameters. The survival rate is higher in patients who did not have arrhythmia when compared to patients who had arrhythmia after adjusting for the effects of other variables. The median survival time is around 7 days for in patients with arrhythmia and around 18 days in patients without arrhythmia. Hazard function shows that patient with arrhythmia had more risk (Blue line) of death when compared to the patients without arrhythmia.

DISCUSSION:

In the present analytical comparative study done in a tertiary care teaching hospital in rural Puducherry, represents the data to describe the impact of COVID-19 infection on the patients presenting with ACS. In our study, the participants were followed up for the duration of their hospital stay, to assess the outcome, all-cause mortality.

Among the various clinical symptoms of ACS, chest pain was the most presenting clinical features among the patients with and without COVID. In our study, chest pain was the most common symptoms presented by the study participants followed by chest pain with breathlessness as a combined symptoms and found to be statistically significance ($p < 0.001$). This was in concordance with the study done by Pandit BN et al, in New Delhi, where most of the study participants presented with chest pain rather than other symptoms.[14] Also, other studies implied that dyspnoea, cough, fever were the clinically presenting symptoms in patients with COVID positive also suggestive of patients with ACS.[14,15] Moreover, many patients were presented with atypical symptoms of ACS in the presence of COVID-19.[14,16] Thus, it is essential that COVID patients presented with typical and atypical symptoms needs to be assessed for cardiovascular findings.

Underlying co-morbidity found among the patients were diabetes (42%), systemic hypertension (15%), chronic kidney disease (0.5%) and diabetes with hypertension (35%) (*p* 0.01) in our study and found to be statistically significant among the ACS patients with and without COVID. The result was in-line with the study done by Pandit BN et al,[14] where 34.8% of COVID positive patients with CVS manifestation were presented with co-morbidities. Other studies which also implied that presence of co-morbidities might leads to the CVS complications.[17–19] The findings from our study and the existing literatures reinforce that in the presence of the pre-existing co-morbidities, the severity of the SARS-COV-2 risk also increased.[9,19–21] Moreover, the prevalence of hypertension and diabetes were found to be higher among these patients.[22,23] The mechanism underlying were unknown, yet postulated

theory include role in renin-angiotensin-aldosterone system in the hypertension dysregulate the system and also due to robust impaired immune system with inflammatory states. This further results in progression of COVID severity and mortality.[14,17,22–24] Henceforth, necessary assessment is required in patients COVID positive with multiple co-morbidities to reduce the severity of the disease.

Cardiovascular markers were widely used to assess the pathological and physiological conditions including ACS or MI among the patients and aid in the treatment plan. The pre-requisite markers held responsible in clinical utility for the cardiac injury were troponin I, CPK NAC and MB. It has been found that increased troponin I and CPK MB and reduced CPK NAC among the ACS patients with COVID-19 when compared to the patients with no COVID in our study. Yet, CPK MB only significant statistically ($p < 0.001$) in our study. A study done by Case BC et al showed that there was an increased level of troponin I of ≥1.0 ng/ml and Chen Q et al showed that 42.6% elevation of Troponin I among the patients with COVID when compared to non-COVID in MI.[19,25] A pooled study conducted showed that troponin were significantly higher that other markers like D-miner, CK, BNP in COVID patients who died or critically ill.[26,27] There were other studies were inflammatory markers also increased during the COVID among the patients with cardiac manifestations.[17,26,28–30] These markers indicate the inflammation or infection and add prognostic value for the determination and triaging of the COVID-19 severity and it can predict the mortality among the patients with COVID.

Arrhythmias is an irregular heart rhythm or beat, where the electrical signals that plays with heart's beat does not work in concurrent. In our study among 17 (8.5%) patients out of 200 (91.5%) presented with arrhythmia. It has been observed that cardiac arrhythmia was common among patients with severe COVID patients. It has been considered as one of the complications of the COVID.[15,31,32] The pathophysiology lies behind this might be due to change in ion channels which affected by COVID-19, lead to cardiac repolarization or conduction properties and calcium handling process.[32] Added to that, any type of arrhythmia can result in 30-day mortality among these patients with or without COVID. At time, this arrhythmias are likely the consequence of the systemic illness and not solely the direct effects of COVID-19 infection, which was understood by the multiorgan impact of COVID.[19,33] Consequently, patients with cardiac manifestation, it is essential to assess the risk factors, especially pertaining to the cause of arrhythmia to prevent the overall mortality and also early intervention like CABG, PCI, might help these patients to overcome the complications.

The overall mortality of the study participants was assessed due to cardiac manifestation were 8.5% (17 patients died), among them eight patients where the COVID positive and nine patients were COVID negative. There was a statistical significance found between these two groups (p 0.008). These findings were similar to the study done by Pandit et al, where the all-cause mortality was 3.9% among the COVID patients.[14] Study done by Case BC et al, showed that the in-hospital mortality was increased to 48.4% in patients with ACS and COVID.[17] There are other literature which implies about 2.5 to 40% cardiac manifestation with COVID had all-cause mortality within maximum of 30 days.[16–18,34–36] Milovancev et al[37] did a survival study on the patients with coronary risk group and COVID to understand the mortality, where the survival rate of these patients were reduced due to the presence of COVID which acts as a concomitant factor and aid in poor prognosis. It was similar to our study findings, where the survival analysis showed arrhythmia in the presence of COVID reduce the survival rate of the patients. Addition to that, the likelihood of the death was due to multiorgan failure with the presence of the other risk factors. Early diagnosis and management of the patients in ICU needs to do to prevent the mortality and the healthcare providers need to be aware that ACS with COVID were fatal combination, ends up with poor prognosis.

Though there many strengths in our study, there were few limitations. Since, this study is a single-centred study, might not represent the impact of the COVID-19 in other settings especially primary care settings. The patients were followed up for the period of hospital stay only which might compromise the result. Added to that, patients who underwent CABG, or PCI and other interventions and the vessel responsible for the MI were not captured to understand the underlying aetiology. Since, the sample size is small, it warrants the study with larger sample size to generalize the results. However, being a cross-sectional comparative study, temporality of association could not be assessed.

CONCLUSION:

ACS patients in COVID-19 infection presented with high burden of cardiovascular complication with higher mortality, especially in patients with the presence of arrhythmia. Thus, it implies that COVID-19 in ACS patients can substantially led to higher in-hospital mortality. Henceforth it is recommended that efforts should be focused, by recognising the cardiovascular complication at the earliest among the patients presenting with COVID-19 irrespective of the severity and to treat appropriately reduce the mortality.

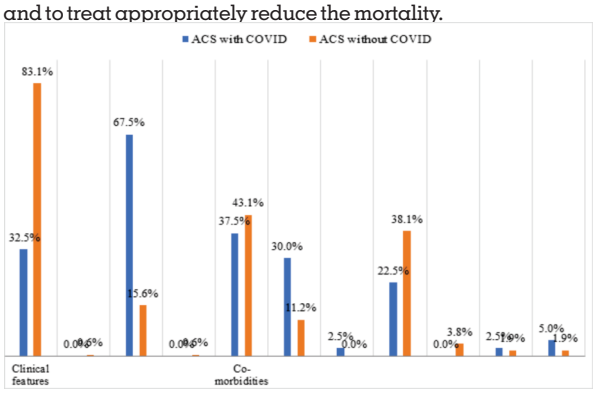

Figure 1: Clinical features and co-morbidity of the ACS study participants with and without COVID (N = 200)

Table 1: Laboratory values of acute coronary syndrome in patients overall and based on COVID-19 status (N = 200)

Variables	Total (N = 200) Mean ± SD	ACS with COVID (n = 40) Mean ± SD	ACS without COVID (n = 160) Mean ± SD	p-value*
Troponin I (ng/L)	4665.75 ± 11268.17	6139.93 ± 11682.20	4297.21 ± 11169.434	0.356
CPK NAC (mcg/L)	298.4 ± 585.831	195.70 ± 408.65	324.08 ± 620.69	0.216
CPK – MB (IU/L)	119.64 ± 212.578	306.45 ± 400.16	72.94 ± 79.414	**<0.001**

*Independent t-test: continuous and parametric; *p* value <0.05 is statistically significant indicated by boldface.

Table 2: Outcome of the acute coronary syndrome in patients overall and based on COVID-19 status (N = 200)

Variables	ACS with COVID (n = 40) n (%) / mean ± SD	ACS without COVID (n = 160) n (%) / mean ± SD	Test; p-value* (95% CI)
Arrhythmia			
Present	4 (23.5)	13 (76.5)	0.145$; 0.704 (0.387 – 4.082)
Absent	36 (19.7)	147 (80.3)	
Ejection fraction (%)	46.60 ± 13.24	50.75 ± 11.76	-1.945#; 0.053 (-8.359 – 0.059)

Mortality	8 (47.1)	9 (52.9)	4.194$; 0.008 (1.504–11.701)

#Independent t-test; $Pearson's chi-square; *p value <0.05 is statistically significant indicated by boldface.

Table 3: Comparison of median survival time in days across ACS patients with arrhythmia using Kaplan-Meier estimation.

Arrhythmia status	Total no. of patients n (%)	No. of events occurred n (%)	Median survival time (days)	95% CI
Present	17 (8.5)	7 (41.2)	10	6.607 – 13.393
Absent	183 (91.5)	10 (5.46)	18	15.14 – 17.89

*p value <0.05 based on Log-rank, Breslow, and Tarone-ware; CI – Confidence Interval

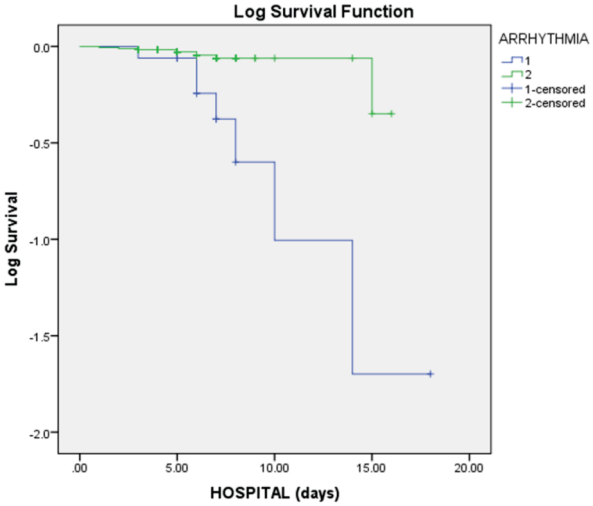

Figure 2: Comparison of the survival time in days across patients with presence of arrhythmias using Kaplan-Meier plot (N = 200)

Table 4: Cox-proportional hazards regression analysis of the effect of COVID status, 2D ECHO, laboratory parameters and the status of arrhythmia in mortality of ACS patients (N = 200)

Variables	n (%)	Unadjusted hazard ratio; p value; 95% CI	Adjusted hazard ratio; p value; 95% CI
COVID-19 status			
Positive	40 (20.0)	2.516; 0.158 (0.698 – 9.070)	1.754; 0.349 (0.541 – 5.681)
Negative	160 (80.0)	1	1
Arrhythmia			
Present	17 (8.5)	5.198; 0.003 (1.765 – 15.307)	4.291; 0.006 (1.507 – 12.215)
Absent	183 (91.5)	1	1
2D ECHO			
RWMA	180 (90.0)	2.695; 0.430 (0.230 – 31.611)	0.956; 0.966 (0.120 – 7.603)
Normal study	20 (10.0)	1	1

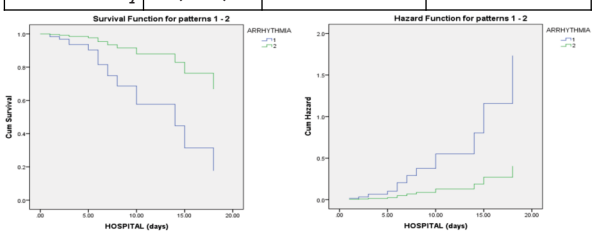

Figure 3: Adjusted survival curve and hazard function for the ACS patients after adjusting other variables.

REFERENCES:

1. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2022 Sep 27]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/index.html
2. Liu YC, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. Biomed J. 2020 Aug;43(4):328–33.
3. Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, Farahmandian N, Miresmaeili SM, Bahreini E. A comprehensive review of COVID-19 characteristics. Biol Proced Online. 2020 Aug 4;22(1):19.
4. WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2022 Sep 25]. Available from: https://covid19.who.int
5. Basu-Ray I, Almaddah N k, Adeboye A, Soos MP. Cardiac Manifestations Of Coronavirus (COVID-19) [Internet]. StatPearls [Internet]. StatPearls Publishing; 2022 [cited 2022 Oct 14]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556152/
6. Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the Cardiologist. JACC Basic Transl Sci. 2020 Apr 10;5(5):518–36.
7. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020 Jul;5(7):802–10.
8. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531–8.
9. 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. Lancet Lond Engl. 2020;395(10223):497–506.
10. ACC Clinical Bulletin Focuses on Cardiac Implications of Coronavirus (COVID-19) [Internet]. American College of Cardiology. [cited 2022 Oct 14]. Available from: https://www.acc.org/latest-in-cardiology/articles/2020/02/13/12/42/http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2farticles%2f2020%2f02%2f13%2f12%2f42%2facc-clinical-bulletin-focuses-on-cardiac-implications-of-coronavirus-2019-ncov%3freport%3dreader
11. Magadum A, Kishore R. Cardiovascular Manifestations of COVID-19 Infection. Cells. 2020 Nov 19;9(11):2508.
12. Schiavone M, Gobbi C, Biondi-Zoccai G, D'Ascenzo F, Palazzuoli A, Gasperetti A, et al. Acute Coronary Syndromes and Covid-19: Exploring the Uncertainties. J Clin Med. 2020 Jun 2;9(6):1683.
13. Statistics and Sample Size Pro – Apps on Google Play [Internet]. [cited 2022 Nov 17]. Available from: https://play.google.com/store/apps/details?id=thaithanhtruc.info.sass&hl=en_IN&gl=US
14. Pandit BN, Shrivastava A, Nath RK, Kuber D, Sinha SK, Aggarwal P. Impact of COVID-19 on Thrombus Burden and Outcome in Acute Myocardial Infarction. Cureus. 2021 Aug;13(8):e16817.
15. Capaccione KM, Leb JS, D'souza B, Utukuri P, Salvatore MM. Acute myocardial infarction secondary to COVID-19 infection: A case report and review of the literature. Clin Imaging. 2021 Apr;72:178–82.
16. Solano-López J, Zamorano JL, Pardo Sanz A, Amat-Santos I, Sarnago F, Gutiérrez Ibañes E, et al. Risk factors for in-hospital mortality in patients with acute myocardial infarction during the COVID-19 outbreak. Rev Espanola Cardiol Engl Ed. 2020 Dec;73(12):985–93.
17. Case BC, Yerasi C, Forrestal BJ, Shea C, Rappaport H, Medranda GA, et al. Comparison of Characteristics and Outcomes of Patients With Acute Myocardial Infarction With Versus Without Coronarvirus-19. Am J Cardiol. 2021 Apr 1;144:8–12.
18. Modin D, Claggett B, Sindet-Pedersen C, Lassen MCH, Skaarup KG, Jensen JUS, et al. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. Circulation. 2020 Nov 24;142(21):2080–2.
19. Case BC, Yerasi C, Forrestal BJ, Shea C, Rappaport H, Medranda GA, et al. Clinical Impact and Predictors of Troponin Elevation in Patients With COVID-19. Cardiovasc Revascularization Med Mol Interv. 2021 Dec;33:41–4.
20. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020 Jul 23;383(4):334–46.
21. Cao M, Zhang D, Wang Y, Lu Y, Zhu X, Li Y, et al. Clinical Features of Patients Infected with the 2019 Novel Coronavirus (COVID-19) in Shanghai, China [Internet]. medRxiv; 2020 [cited 2022 Dec 1]. p. 2020.03.04.20030395. Available from: https://www.medrxiv.org/content/10.1101/2020.03.04.20030395v1
22. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, et al. SARS-CoV2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19? Eur Heart J. 2020 May 14;41(19):1801–3.
23. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020 Apr 1;8(4):e21.
24. Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly AM. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. Lancet Lond Engl. 2021 Aug 14;398(10300):599–607.
25. Chen Q, Xu L, Dai Y, Ling Y, Mao J, Qian J, et al. Cardiovascular manifestations in severe and critical patients with COVID-19. Clin Cardiol. 2020;43(7):796–802.
26. Dawson D, Dominic P, Sheth A, Modi M. Prognostic value of Cardiac Biomarkers in COVID-19 Infection: A Meta-analysis. Res Sq. 2020 Jun 13;rs.3.rs-34729.
27. An W, Kang JS, Wang Q, Kim TE. Cardiac biomarkers and COVID-19: A systematic review and meta-analysis. J Infect Public Health. 2021 Sep 1;14(9):1191–7.
28. De Luca G, Debel N, Cercek M, Jensen LO, Vavlukis M, Calmac L, et al. Impact of SARS-CoV-2 positivity on clinical outcome among STEMI patients undergoing mechanical reperfusion: Insights from the ISACS STEMI COVID 19 registry. Atherosclerosis. 2021 Sep 1;332:48–54.
29. Matsushita K, Hess S, Marchandot B, Sato C, Truong DP, Kim NT, et al. Clinical features of patients with acute coronary syndrome during the COVID-19 pandemic. J Thromb Thrombolysis. 2021 Jul;52(1):95–104.

30. Patil R, Das B, Bhatia SY. Cardiac Biomarkers in Patients with COVID-19. Indian J Med Biochem. 2021 Jan 5;24(2):43–9.
31. Linschoten M, Peters S, van Smeden M, Jewbali LS, Schaap J, Siebelink HM, et al. Cardiac complications in patients hospitalised with COVID-19. Eur Heart J Acute Cardiovasc Care. 2020 Dec;9(8):817–23.
32. Wang Y, Wang Z, Tse G, Zhang L, Wan EY, Guo Y, et al. Cardiac arrhythmias in patients with COVID-19. J Arrhythmia. 2020 Oct;36(5):827–36.
33. Bhatla A, Mayer MM, Adusumalli S, Hyman MC, Oh E, Tierney A, et al. COVID-19 and cardiac arrhythmias. Heart Rhythm. 2020 Sep 1;17(9):1439–44.
34. Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Lane DA, Lip GYH. Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients. Eur J Clin Invest. 2021 Nov;51(11):e13679.
35. Rashid M, Timmis A, Kinnaird T, Curzen N, Zaman A, Shoaib A, et al. Racial differences in management and outcomes of acute myocardial infarction during COVID-19 pandemic. Heart Br Card Soc. 2021 May;107(9):734–40.
36. Salinas P, Travieso A, Vergara-Uzcategui C, Tirado-Conte G, Macaya F, Mejía-Rentería H, et al. Clinical Profile and 30-Day Mortality of Invasively Managed Patients with Suspected Acute Coronary Syndrome During the COVID-19 Outbreak. Int Heart J. 2021 Mar 30;62(2):274–81.
37. Milovančev A, Petrović M, Popadić V, Miljković T, Klašnja S, Djuran P, et al. Characteristics and Outcomes of Patients with Acute Coronary Syndrome and COVID-19. J Clin Med. 2022 Mar 24;11(7):1791.