THE EFFECT OF POST-CORONAVIRUS SYNDROME ON A PATIENT'S CARDIOVASCULAR SYSTEM

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Abstract: The objective of this research article is to provide an informed understanding on whether there is a direct correlation of the covid-19 viral infection and whether the implications of this viral infection can have an effect on the cardiovascular system, in specifically we will be analysing and researching the effect within those individuals who have recovered from the covid-19 infection. In addition to this, previous studies have shown a direct relationship between the covid-19 infection and the functional ability of the cardiovascular system with several different co-morbidities arising and various different markers which were analysed in order to gather a definitive diagnosis. The method utilized within this study was intended to take an un-biased and randomized sample of post covid-19 patients who had recovered from the viral infection 6 months from the onset of the coronavirus infection and via the utilization of different procedures such as ; echocardiography, biochemical lab testing, cardiac related stress tests and ultastrucutral and genomic analysis to determine whether there had been a significant adverse reaction of the cardiovascular system in terms of it's effectiveness and efficacy. Within the study, all participants were stratified according to age, height, weight and body mass index in order to make the results credible and un-biased. From a sample of 50 post-covid recovered indidviduals, upon noting the relevant factors we saw that there was a direct relationship between the body mass index and the risk of increase cardiac co-morbidities as those patients who ranged from 28-35 as a reading for their body mass index were suffering from more co-morbidities directly from the covid infection such as ; hypertension, myocardial infarction, myocarditis, myocardial hypertrophy and valvular regurgitations as compared to those individuals who ranged from 19-25 as a reading for body mass index displayed no cardiac related symptoms, from the sample of people investigated they had suffered no cardiac related co-morbidities before the onset of their covid infection and had no genetically related cardiovascular history. In addition to this, on day 14 of post-covid recovery over 70% of individuals included in the sample reported complaints of chest tightness, angina, dyspnoea and excessive diaphoresis. Furthermore, on routine biochemical investigations it was noted the most prominent increase in cardiac biomarkers were displayed on days 6 and 18 upon medical discharge from the hospital and in specifically we saw an increase in cardiac biomarkers ; creatine-kinase-MB, troponin-t and troponin-I which were all elevated two-fold out of the normal indicated reference ranges. To summarize, from all the resultant data collected we can state there is a generalized link between the covid-19 viral infection and the effect this viral infection can have on the cardiovascular system due to the clinical presentation of many cardiovascular related abnormalities in patients who had no previous medical history, however, more research needs to be done in order to understand the pathophysiological mechanisms behind this relationship in order to make a definitive link between coronavirus and the cardiac-related complications presented in patients.
Keywords: covid-19, biomarkers, cardiac, imaging, symptoms.

1. INTRODUCTION

To evaluate the effect of post-covid syndrome on patients and the effect if any, on the cardiovascular system. The intended target audience of this review article is for those who either have a background in cardiology/physiology or for those individuals who have a wider expressed interest in the medical discipline. The various sources/journals that have been used to construct this review article are indeed appropriate for the objective we will be evaluating. In addition this article will be a review of the sources cited at the beginning of this article. This article will be an empirical view based upon the clinical findings and observations of various renowned researchers as well as my own research.

Cardiovascular diseases in addition with the exposure to the SARS-Cov-19 infection can lead to a combination of a wider range of serious side effects which can be further aggrevated by risk factors such as ; Age/Sex/ High-Obesity/BMI/Hypertension. These wide range of risk factors mentioned can lead to a higher probability of cardiovascular diseases as we know with an increase in age we have weakening of the cardiovascular apparatus i.e. papillary muscles, tendon chordinae, heart valves. In addition to this according to statistics, males are at a 47% higher chance of developing cardiovascular related diseases indicating the sex of an individual plays a pivotal role in the development of cardiovascular diseases. Furthermore, both statistically and clinically it has been revealed that a diet rich in lipids and fats are of a higher probability to lead to cardiovascular related syndromes, this is due to the fact that a diet which is higher in lipids can lead to arthesclerotic events further precipitating as coronary artery diseases which can lead to myocardial ischemia and finally congestive heart failure or sudden cardiac death. A diet

rich in lipids can also exceed the uptake threshold of tissues from lipids circulating in the systemic circulation leading to more lipids freely able to move in the bloodstream and eventually due to the increase in intake of fats not being balanced by the breakdown and utilisation of fats they can precipitate on the heart's valvular structures leading to a rigid and a stiffer heart which leads to hypertrophy and insufficiency of the heart to meet the oxygen demands of the body, thereby limiting the heart's ability to meet the cardiac output of the heart. According to statistics, it states that the body has the ability to absorbs fats within a time period of 5 hours from the intake of ingested foods until the tenth hour at which the absorption and breakdown of fats is reduced from 80% to 30%. All of these aggravating factors are important to mention as upon exposure of the bodily systems to SARS-Cov-19, due to aforementioned factors the risk of SARS-Cov-19 is 45% more likely to cause cardiac related co-morbidities such as myocardial fibrosis and myocardial oedema.

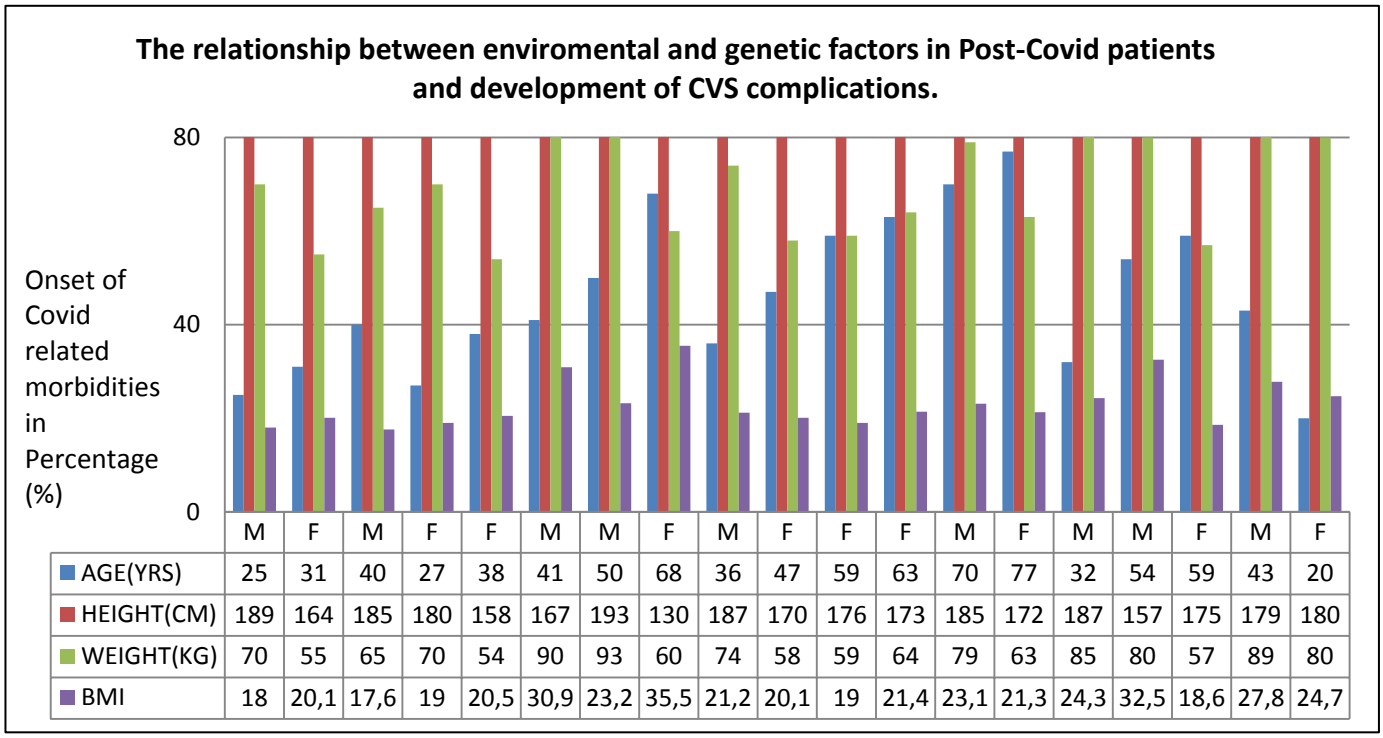
2. MATERIALS AND METHODS

In our study on the ACE-2 expression in the adult human, hearts from both healthy and deceased patients were taken to illuminate the potential capacity of the heart being infected by SARS-Cov-19. Firstly, the donated heart underwent isolation of the myocardial nuclei and the nuclei were purified using a 5% sucrose buffer solution. Then a single RNA-sequencing method was utilised to process the material and after single-data cell analysis, the top 150 variable genes underwent principal component analysis and this served as an input for 2D visualizations which were identified by T-distributed stochastic neighbour embedded plot. The cell types were identified utilising a cell-ligand identified marker and the cell-cell interactions were weighted by product of fold changes of ligands in sender-cell types and fold change in corresponding receiver-cell types. The total RNA extracted from frozen tissue and used for library construction followed by Hi-sequencing and the gene expressions were recorded as transcripts per nuclei and students T-test were compared between two groups. The proteomic analysis is based upon ligand chromatography-tandem mass spectrometry and 8 fallen hearts and 8 normal heart donors were prepared for protein profiling utilising TNT strategy. The spatial confirmation of receptor-binding domains was identified of spike and human ACE-2 utilising software related target-tandem alignment.

3. RESULTS

The results showcased based upon modelling and docking the spike protein has a tight conformational shape to that of ACE-2 and the specific residues; 44Leu/472Pha/479Gla/480Ser/487Asn/491Tyr of mature spike proteins is integral for effective and efficient binding. Screening ACE-2 Mrna expression via human organs based upon a GTFrx database indicates that the heart has a higher level of ACE-2 expression than the lungs. Analysis of myocardial cell constitution via the presence of nuclease trancriptome analysis and then we are able to observe out of all the ACE-2 expression in the myocardium over 80% is expressed in the myocardial pericytes. The pericytes are also not only confined to the myocardium but it is also found and extended out to the endothelial cells and capillaries/venules indicating that it can also affect the myocardial micro-circulation. Finally, the pericytes are ligand-secreting cells and calculation of each receptor-ligand interaction indicates that the pericytes are ligand secreting cells and it was found that neutrophils and endothelial cells are the most favourable in terms of interaction with the pericytes. The ratios between AngPT1: AngPT2 indicates that pericytes are essential in determining the endothelial cell membrane stability and SARS-Cov-19 can attack the pericytes enhancing a further endothelial cell dysfunction, inducing micro-circulatory disorders. On the contrary those patients who had previously suffered from the SARS-Cov-19 infection and have heart co-morbidities were seen to have a higher susceptibility to the covid infection and therefore further aggravation of pre-existing cardiac injuries. The below diagram is a representation of different factors taken into consideration of post-covid patients and whether there is any relationship between the factors: age, height, weight and BMI and increased likelihood of development of cardiovascular complications. It has been reported that an increase in BMI in post-covid patients leads to a 44% increase risk for development in cardiovascular complications such as coronary artery disease, hypertension and myocardial infarction. We can see in an unbiased random sample of 20 post-covid patients, that there is a direct correlation between the age and weight of an individual. There is a direct pattern indicating the greater the age and weight in comparison to the standard we have an increase in BMI which is a strong indication for the development of post-covid cardiovascular complications. In addition to this, we discovered that gender also plays a role in development of cardiovascular-related diseases as males were at a higher risk to the development of cardiovascular diseases then females. In addition to this the BMI (body mass index) as an individual variable, indicated that across the subjects sampled generally the higher the BMI the more increase likeliness of early onset of covid-19 related cardiovascular co-morbidities. This is due to the fact that in relation to BMI being a marker for obesity, the more obese you are the higher risk of developing arthesclerotic complications which can lead to secondary complications such as ; myocardial hypertrophy, valvular calcifications, myocarditis and myocardial ischemia. In addition to this 60% of the

subjects in the sample with a higher BMI suffered from one or more of the latter cardiovascular complications. Overall, the results show some strong links between covid-19 and the effect it can have on the cardiovascular system, however, a larger sample is needed in order to obtain a broader understanding and to have a clear



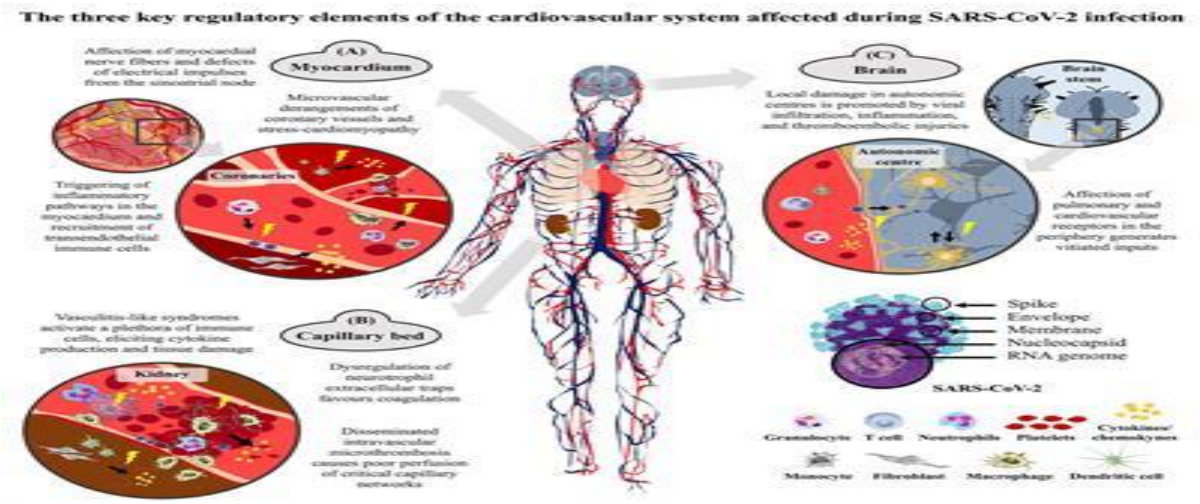
	M	F	M	F	F	M	M	F	M	F	F	F	M	F	M	M	F	M	F
AGE(YRS)	25	31	40	27	38	41	50	68	36	47	59	63	70	77	32	54	59	43	20
HEIGHT(CM)	189	164	185	180	158	167	193	130	187	170	176	173	185	172	187	157	175	179	180
WEIGHT(KG)	70	55	65	70	54	90	93	60	74	58	59	64	79	63	85	80	57	89	80
BMI	18	20,1	17,6	19	20,5	30,9	23,2	35,5	21,2	20,1	19	21,4	23,1	21,3	24,3	32,5	18,6	27,8	24,7

Figure 1: A bar histogram representing the relationship between age, height, weight, BMI and the influence of these variables on the development of covid-19 within randomized patients.

4. DISCUSSION

The below diagram showcases the key regulatory elements of the cardiovascular system that are compromised upon exposure to SARS-Covid19. The myocardium is affected by the activation of the inflammatory pathways and involvement of trans-endothelial immune cells, also we have on a micro-vascular level a complete derangement of the capillary bed and its associated vascular networks which in turn lead to the existence of defects in the neuro-electrical impulses generated in the intra-atrial septum via the sino atrial node. SARS-Covid-19 can also affect the brain via penetrating the blood brain barrier and in this situation we have cardiovascular receptors located in the peripheral of the left lateral cerebral hemisphere which can be triggered into a state of affection leading to the generation of vitalized impulses. Finally, the covid-19 infection can lead to a clinical situation called intravascular micro thrombosis whereby the viral particles causes thrombus formation in the major arteries and via haematogenous dissemination it travels to affect the coronary/capillary vessels in the heart compromising the blood circulation and ejection fraction of the heart. In addition to this, the pathophysiological mechanism of the process in which SARS-Cov-19 affects the cardioavascular system is clearly understood. Firstly, we have the presence of angiostensin-2 receptors in the myocardium of the heart. About 2 million angiotensin-2 receptors are completely recycled and regenerated in the heart. The main target for SARS-Cov-19 is the angiotensin-2 receptors. These receptors are an attachment site for the entry of viral covid particles and essentially in the ultra-structure of the covid particle we have viral spike proteins on the outer membrane of the viral particle which binds to the specific complementary site on the angiotensin-2 receptor accompanied by the protein TMPRSS2 which plays a pivotal role in increasing the affinity between the two structures.

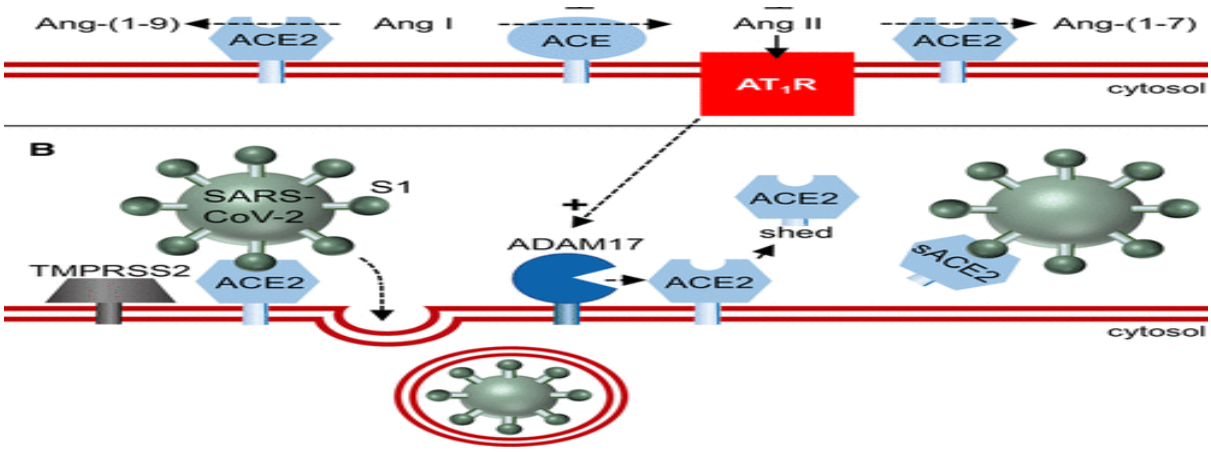
Figure 2: Showcasing the 3 key regulatory elements of the cardiovascular system affected during a covid-19 infection.



Generally, ACE-2 exist in the renin-angiotensin-aldosterone-system via blood pressure regulation and the electrolyte homeostasis and these specific types of effects are exerted by the angiotensin-2 type 1 receptors via reducing inflammation, increasing blood pressure, aldosterone synthesis, potassium excretion, renal sodium reabsorption and vasoconstriction. ACE-2 is responsible for the degradation of angiotensin-2 into angiotensinogen. Generally, the process involves the inhalation of viral SARS-Cov-19 viral particles and then it passes the mucous membrane of the upper respiratory tract and can enter the peripheral bloodstream via lungs stimulating the process of viremia and leading to extra-luminal spread which can progress to nearby organs such as the heart affecting its cardiovascular functions via inhibition of the angiotensin-2 type 1 receptors mainly in the pericytes rather than the cardiomyocytes. The ACE-2 plays a pivotal role for the entry of viral particles into myocardial cells and in a study it has been found that the SARS-Cov-19 infection can lead to a heart infection which is associated with myocardial inflammation and interstitial fibrosis and within the sample of post-covid patients who were sampled after a period of 6 months of recovery from coronavirus-19 infection there had been around a 44% increase in cardiovascular related disorders of mainly constituted by two types ; acute myocardial Injury and arthersclero-embolic related events.

Below illustrated is a diagram representing the proposed mechanism of covid-19 viral particles and it's inhibition of the angiotensin-2 receptors. The diagram (A) indicates to us the normal physiological situation when we have no presence of SARS-Cov-19 particles we can see the ACE molecule cleaving the angiotensin 1-9 and in specifically when ACE causes conversion of angiotensin 1 into angiotensin 2 we have the binding of ACE inhibitors to the ACE molecule thereby inactivating the molecule. Then we have the conversion of angiotensin-2 into angiotensin 1-7 via the ACE-2 molecule and thereby inactivation of the angiotensin-2 receptor via the angiotensin receptor blockers and causing the conversion of angiotensin-2 into a protein receptor called ADAM-17. Furthermore, in diagram (B) the viral particles of SARS-Cov-19 are bound to the ACE-2 receptor and via a cleft in the membrane it is exocytose out of the cytosol and into the extracellular matrix/surroundings. Another mechanism is via the ADAM-17 membrane protein cleaving the ACE-2 molecular receptor from the cytosolic membrane leading to the shedding of the receptor and inhibiting the interaction between the SARS-Cov-19 particle and the ACE-2 receptor.

Figure 3: An illustration presenting the interaction between Covid-19 viral particles and ACE-2/angiotensin receptors.



Furthermore, the infection of SARS-Cov-19 within an individual is likely to elicit a series of secretions of cytokines from cardiac fibroblasts to increase the inflammatory reaction and the recruitment of transendothelial monocytes and the neutrophils and dendritic cells. The activated dendritic cell leads to a further activation of T-cells promoting further tissue damage. The endothelial dysfunction leads to a likely prognosis of acute myocardial injury and acute myocarditis which is understood as the viral particles increase in concentration within the systemic circulation it leads to an increase in viral shedding into the blood flow leading to some particles directly affecting the endothelium and we have the so called "Two-activation theory of the endothelium." The first theory outlines the release of inflammatory cytokines which trigger the activation of inflammatory pathways whereby the activation of the platelet and exocytosis of aberrant coagulation trigger the activation of microthrombocytic pathways. SARS-Cov-19 are known to affect homeostasis with their ability to agglutinate platelets, causing haemolysis and leading to the formation of pro-coagulant complexes with antibodies enabling infiltration into the myocardium and the aberrant coagulation is the underlying mechanism for ischaemic heart disease/stroke/venous thromboembolism. The second theory is whereby the SARS-Cov-19 is likely to alter the immune cellular response and fibronolytic system in particularly the neutrophil extracellular traps which are utilised to trap viral-like structures thus facilitating the cleavage by macrophages and if the neutrophils are aberrantly aggregated it can lead to capillary destruction. If this occurs it can lead to distant re-circulation of material and the risk of distant thrombi-associated vascular damage and thus halt in the small coronary vessels leading to acute myocardial injury (Dixit, 2021).

One of the main cardiovascular complications caused by Post-Covid syndrome within patients is found to be the acute myocardial injury and it is induced by the following sequence of stages; Firstly, we have the inhalation of the viral particles of covid which is then taken in via the lungs affecting the respiratory system and by further haematogenous dissemination it can affect the heart. Next, we have hyper inflammation and cytokine mediated immune response induced by the pathologic T-cells/Monocytes leading to myocarditis. In addition the compromised respiratory system can directly induce hypoxemia reducing the amount of oxygen within the systemic circulation leading to a direct damage of the cardiac myocytes and in specifically the cardiac pericytes which leads to down-regulation of ACE-2 expression and subsequent signalling pathways within the cardiac myocytes. This down regulation and damage of cardiac myocytes can lead to hypercoagubility and the development of coronary micro-vascular thrombosis. We also have diffuse endothelial injury and endothelitis within the heart due to the viral involvement which stimulates a further autoimmune response by the bodily immune system. Finally, an inflammatory response/stress of a coronary artery plaque rupture or ventilation/perfusion mismatches which in the long term can lead to chronic myocardial infarction. In 44,000 post-covid patients the most common repeated co-morbidities include the so called hypertension and cardiovascular disease and are explained by the increase or decrease in expression of ACE-2 and a shift in ACE2/ACE in both directions (Bavishi, 2019, p. 683).The most typical cardiovascular related symptoms arising with relation to SARS-Cov-19 infection are as follows; chest tightness, Dizziness, chest pain, increase in the resting heart rate, heart palpitations. In addition to this as mentioned before myocarditis is one of the most evident cardiovascular complications arising from infection with covid-19. The myocarditis was reported in the mid 2020's with radiologists witnessing an alarmingly high prevalence of imaging abnormalities suggestive of myocardial inflammation and myocardial injury. In a study of 29 patients

previously hospitalized with covid-19 and show elevated troponin of idiopathic cause had shown a late-gadolinium enhancement in a non-ischemic myocarditis like pattern on cardiac resonance magnetic imaging approximately one month after discharge. The imaging criteria for myocarditis are as follows; Indication of myocardial oedema by T2 mapping and non-ischemic myocardial injury by abnormal T1 signal, extracellular volume or late gadolinium enhancement.

In relation to SARS-Cov-19 we see an elevation of cardiac biomarkers which acts as an useful aid to prevent deterioration and potentially guide in therapy including the intensity of anti-coagulants whilst not causing a remission of the viral covid-19 infection and examples of the most common cardiac biomarkers include ; CK-Kinase, troponin-T, troponin-I. Of 192 patients there was an increase of 17% HS-troponin. In the non-survivors the HS-troponin was elevated 16 days after the disease of onset in elevation with LDH/IL-6/D-Dimer (Mueller, 2021, p.315).Conducting a pooled analysis of the several different cardiac biomarkers showcased that upon undertaking laboratory examination, 93% of patients who experienced chest pain or chest tightness due to SARS-Cov-19 infection had a poor prognosis which include some of the common co-morbidities such as ; pericarditis, heart failure, coagulopathies, cardiac shock, arrhythmias, liver injuries, acute distress respiratory syndrome, acute kidney injuries. In specifically, the cardiac troponin is a quantitative marker it should be seen clinically in patients as a combination between the presence or extent of pre-existing cardiac disease and the acute myocardial injury related to post-covid 19 and the related complications and the evidence from clinical studies showed that about 10-20% of patients who were in the recovery stages of covid-19 indicated increased levels of cardiac troponin however the concentrations of cardiac troponin greatly remained in the normal ranges for covid-19 survivors. These elevations in biomarkers were seen in particular with old patients suffering from a pre-existing cardiovascular related disease in conjunction with acute myocardial injury related to covid-19 (Mueller, 2021).

5. CONCLUSION

Overall, covid-19 as it is known today is a multifaceted illness which is comprised of several different complications which stem from a biological nature including hypoxemia, ischemic/non-ischemic injuries, central nervous system dysfunctions, dysrhythmias. Given the latter forms of complications arising from covid-19, it is quite sensible to conclude that the more autonomic dysfunctions of critically ill patients, the more difficult and complex is the preservation of haemodynamic balances thereby increasing the likelihood of cardiovascular complications from covid-19 or chronic cardiac damages in those patients who survive. In terms of treatment, electrophysiological monitoring may be useful for monitoring and providing care for the patient but drugs for the treatment of covid-19 have not been developed yet. Clinical trials for therapies such as immunotherapies, extracorporeal membrane oxygenation and heparin-induced anticoagulant therapy are currently being tested for efficacy and effectiveness.

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