"TO STUDY THE SERUM ANGIOTENSIN CONVERTING ENZYME LEVEL (ACE) AS A POSSIBLE BIOMARKER IN COVID-19:" A ONE YEAR CROSS SECTIONAL STUDY AT A TERTIARY CARE HOSPITAL."

BY

REG NO: BG0120007

Dissertation

Submitted to

KAHER, Belagavi, Karnataka,

In partial fulfilment of the requirements for the degree of

M.D.

IN

GENERAL MEDICINE

JAWAHARLAL NEHRU MEDICAL COLLEGE,

KAHER, BELAGAVI – 590010 KARNATAKA.

JUNE/JULY – 2023

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH, BELAGAVI, KARNATAKA.

ENDORSEMENT BY THE HOD/ PRINCIPAL/ HEAD OF THE INSTITUTION

This is to certify that the dissertation **"TO STUDY THE SERUM ANGIOTENSIN CONVERTING ENZYME LEVEL (ACE) AS A POSSIBLE BIOMARKER IN COVID-19:" A ONE YEAR CROSS SECTIONAL STUDY AT A TERTIARY CARE HOSPITAL."** is a bonafide research work done by **REG NO. BG0120007.**

Dr. REKHA S. PATIL MD,
Professor & Head
Department of General Medicine
J.N. Medical College
Nehru Nagar, Belagavi- 590010

Date: 14/01/23
Place: Belagavi

Dr. N. S. MAHANTASHETTI MD,
Principal J.N. Medical College
J.N. Medical College
Nehru Nagar, Belagavi- 590010

PRINCIPAL
J.N. Medical College,
BELAGAVI- 590 010

KAHER BELAGAVI J.N. MEDICAL COLLEGE

Date: 16/01/23
Place: Belagavi

UNDERTAKING

I, **Reg No. BG0120007,** hear by declare that the information and data mentioned in my dissertation entitled **"TO STUDY THE SERUM ANGIOTENSIN CONVERTING ENZYME LEVEL (ACE) AS A POSSIBLE BIOMARKER IN COVID-19:" A ONE YEAR CROSS SECTIONAL STUDY AT A TERTIARY CARE HOSPITAL."** belongs to me and is original. I am aware of the definition of plagiarism as detailed below:

- AN ACT OR INSTANCE OF USING OR CLOSELY IMITATING THE LANGUAGE AND THOUGHTS OF ANOTHER AUTHOR, WITHOUT AUTHORIZATION AND REPRESENTATION OF THAT AUTHORS WORK AS ONE'S OWN, AS BY NOT CREDITING THE ORIGINAL AUTHOR.
- A PIECE OF WRITING OR OTHER WORK REFLECTING SEARCH UNAUTHORIZED USE OR IMITATION.
- THE DELIBERATE OR RECKLESS REPRESENTATION OF ANOTHER'S WORDS, THOUGHTS OR IDEAS AS ONE'S OWN WITHOUT ATTRIBUTION IN CONNECTION WITH SUBMISSION OF ACADEMY, WORK, WHETHER GRADED OR OTHERWISE.

I HEREBY DECLARE THAT THE DISSERTATION PREPARED BY ME IS ORIGINAL-ONE AND DOES NOT INVOLVE PLAGIARISM ANYWHERE. IN CASE AT A LATER STAGE, IT IS FOUND THAT I HAVE INDULGED IN PLAGIARISM, THEN I AM SOLELY RESPONSIBLE FOR THE SAME AND THE INSTITUTION IS AT LIBERTY TO TAKE ANY DISCIPLINARY ACTION AGAINST ME INCLUDING CANCELLATION OF MY DISSERTATION, OR ANY OTHER PENALTIES AS IMPOSED BY THE UNIVERSITY.

Date: 14/01/23

Place: Belagavi

REG NO: BG0120007

ANTI-PLAGIARISM CHECK – ACCEPTANCE LETTER

KLE
JAWAHARLAL NEHRU MEDICAL COLLEGE
(Recognized by Medical Council of India, New Delhi)
Accredited 'A+' Grade by NAAC (3rd Cycle) Placed in Category 'A' by MHRD (GoI)
Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA
0831 - 2471350 0831 - 2470759 www.jnmc.edu principal@jnmc.edu

Ref No: MDC/PG/ Date: 14-12-2022.

ACCEPTANCE LETTER

The softcopy of thesis entitled: "TO STUDY THE SERUM ANGIOTENSIN CONVERTING ENZYME LEVEL (ACE) AS A POSSIBLE BIOMARKER IN COVID-19- A ONE YEAR CROSS SECTIONAL STUDY AT A TERTIARY CARE HOSPITAL."" has been submitted for Anti-Plagiarism check through Turnitin software. The scan has been carried out and the scanned output reveals a match percentage of **06%** which is within the acceptable limits of **10%** as per the guidelines given by UGC.

Guide.

Dr. (Mrs.) N.S. Mahantashetti.
Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

To,
Reg. No. BG0120007,
Postgraduate Student,
2020-21 Batch,
Department of General Medicine,
J. N. Medical College, Belagavi.

ETHICAL CLEARANCE CERTIFICATE

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed to be University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 23 **Date: 25/01/2021**

To,

REG NO: BG0120007

PG student in Medicine,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"TO STUDY THE SERUM ANGIOTENSIN CONVERTING ENZYME LEVEL (ACE) AS A POSSIBLE BIOMARKER IN COVID-19:" A ONE YEAR CROSS SECTIONAL STUDY AT A TERTIARY CARE HOSPITAL.** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Smita Sonoli)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Harsha Hegde)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ABSTRACT

The COVID-19 outbreak has claimed the lives of almost 2 million individuals. In the renin-angiotensin system, angiotensin-converting enzyme 2 (ACE2) is a counter-regulatory enzyme that converts angiotensin-2 to Ang-(1-7) form. Several researches have looked into the relationship between ACE2 and COVID-19. Indeed, the anti-inflammatory/anti-oxidant action of the ACE2/Ang (1-7) system protects the lung from acute respiratory distress syndrome. SARS-Cov-2, on the other hand, can enter host cells via ACE2. ACE2 expression can be changed by a variety of variables, including hypertension, diabetes, and obesity, all of which can worsen COVID-19 infection. Furthermore, because androgens boost ACE-2 expression, males are at a higher risk of COVID-19 infection. Although reported figures showed that COVID-19 infection risks differed significantly between adults the explanation for the disparities remains unknown.

Aims:

To investigate serum angiotensin converting enzyme (ACE) levels as much as feasible Biomarker in patients with covid-19.

Methods and results:

Following permission from the institution's scientific and ethical council, the study was completed. After obtaining written informed consent, all patients who meet the inclusion and exclusion criteria will be recruited in the trial. The study, which lasted from October 1, 2020 to September 30, 2021, enrolled 101 persons in total the ages ranged from 19 to 88, with a mean age of 52.28±14.55 years. Other laboratory

indices such as mean D-dimer levels (2751.8 vs 1110.18; p<0.001), mean interleukin 6 (256.4 vs 90.2; p=0.0065) and mean Hs Reactive protein (160.57 vs 98.97; p=0.0039) were significantly higher among expired patients compared to improved patients. Conversely, mean serum albumin levels were significantly lower among expired patients than improved patients (3.4 vs 3.78; p=0.0057). Other evaluated laboratory markers such as mean serum ACE levels, total bilirubin, direct bilirubin, SGOT, SGPT, alkaline phosphatase, urea, creatinine were comparable between expired and improved patients (p>0.05).

Mean serum ACE levels in our study was 18.33 and was comparable between patients with improved and expired patients. In our study, the odds ratio of serum ACE levels at predicting disease outcome was 1.0 suggesting no effect. Similarly, the AUC for serum ace level is found to be 0.5609 (95% CI: 0.3923-0.7294) in predicting mortality outcome. No significant association between serum ACE levels and CT severity. We observed a significant negative correlation between haemoglobin and serum ACE levels and significant positive correlation between Alkaline phosphatase and serum ACE levels.

Conclusion:

In our study cohort, serum ACE levels between patients with different disease severities based on CT score and disease outcome were comparable. Further, results of our study suggested that serum ACE levels is not a good predictor for mortality outcome. Screening of serum ACE levels may be beneficial in assessing the susceptibility and severity of COVID-19 patients. We further suggest prospective, multicenter studies to evaluate the relationship between serum ACE levels and COVID-19 disease severity and clinical outcome.

LIST OF ABBREVIATIONS

ABCA1-p	-	ATP binding cassette transporter A1 Phosphorylated
ACE2	-	Angiotensin-converting enzyme 2
AngI	-	Angiotensin I
AngII	-	Angiotensin II
AP-1	-	Activator protein 1
APJ	-	Apelin receptor
ARDS	-	Acute respiratory distress syndrome
AT1R	-	Angiotensin I type 1 receptor
BMI	-	Body mass index
COVID-19	-	Coronavirus disease-19
ERK	-	Extracellular signal-regulated kinases
FCS	-	Furin cleavage site
MAPK	-	Mitogen-activated protein kinase
MAS R	-	Mas receptor
MERS	-	Middle East Respiratory Syndrome
MW- Mann	-	Whitney U Test
NF-B	-	Nuclear factor-B
PI3K	-	Phosphatidylinositol-3-Kinase
PKC	-	Protein kinase C
RAAS	-	Renin-angiotensin-aldosterone system
RAT	-	Rapid antigen *test*
ROS	-	Reactive oxygen species
RT-PCR	-	Reverse transcription polymerase chain reaction

SARS-CoV-2	-	Severe acute respiratory syndrome coronavirus 2.
Th1	-	T helper cell 1
VEGF	-	Vascular endothelial growth factor
WHO	-	World Health Organization

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

A new coronavirus epidemic (2019-nCoV) was discovered around the tail end of 2019 in Wuhan, Hubei Province, China [1,2]. The infection has spread worldwide. Compared to the Middle East Respiratory Syndrome (MERS) coronavirus and the severe acute respiratory syndrome coronavirus (SARS-CoV), this virus appears to be far more infectious (MERS-CoV). By June 8, 2020, more than 7 million confirmed coronavirus illness 2019 (COVID-19) cases were reported with almost 400,000 fatalities worldwide. Based on Full-length genome sequencing 2019-nCoV and SARS-CoV have 80% similar sequencing, and this similarity was further confirmed by a pairwise protein sequence analysis [2]. Both these viruses enter the host cell through the angiotensin-converting enzyme 2 (ACE2) receptor[3]. This virus later received the new moniker SARS-CoV-2 as a result. Compared to previous infections such as SARS and MERS, the overall mortality rate of COVID-19 is lower; however, severe cases usually involve organ dysfunction, such as acute respiratory distress syndrome (ARDS), cardiac, renal and liver complications. While the renin angiotensin system playa a major role in pathogenesis of many disorders, the expression of angiotensin converting enzyme-2 (ACE2) in humans has proven beneficial. [4-6] Given that both SARS-CoV and SARS-spike CoV-2's proteins interact with ACE2, the patho-physiology of SARS and COVID-19 appears similar. The pathogenesis is greatly aided by the functional receptor of SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2), which allows for viral entrance into human cells [7,8] Moreover, the viral spike (S) protein of virus has more than 10-fold higher affinity to ACE2 receptor making the virus more pathogenic[8,9]. This binding allows the virus to enter the host cell together with the priming of the S-protein by the TMPRSS2 of the host cell. There is no doubt that SARS-CoV-2 cell entry and its pathological effects

mostly damage cells in the (upper) respiratory tract [10,11]. Local ACE2 expression may be connected to further host dispersion, such as in the kidneys or gastrointestinal system (Figure 1).

We investigated ACE2 and SARSCoV-2's participation in the pathophysiology of organ damage in COVID19 since determining their precise roles in the illness may have significant consequences for comprehending the condition. We also describe a number of COVID-19 therapeutic approaches that are currently under consideration.

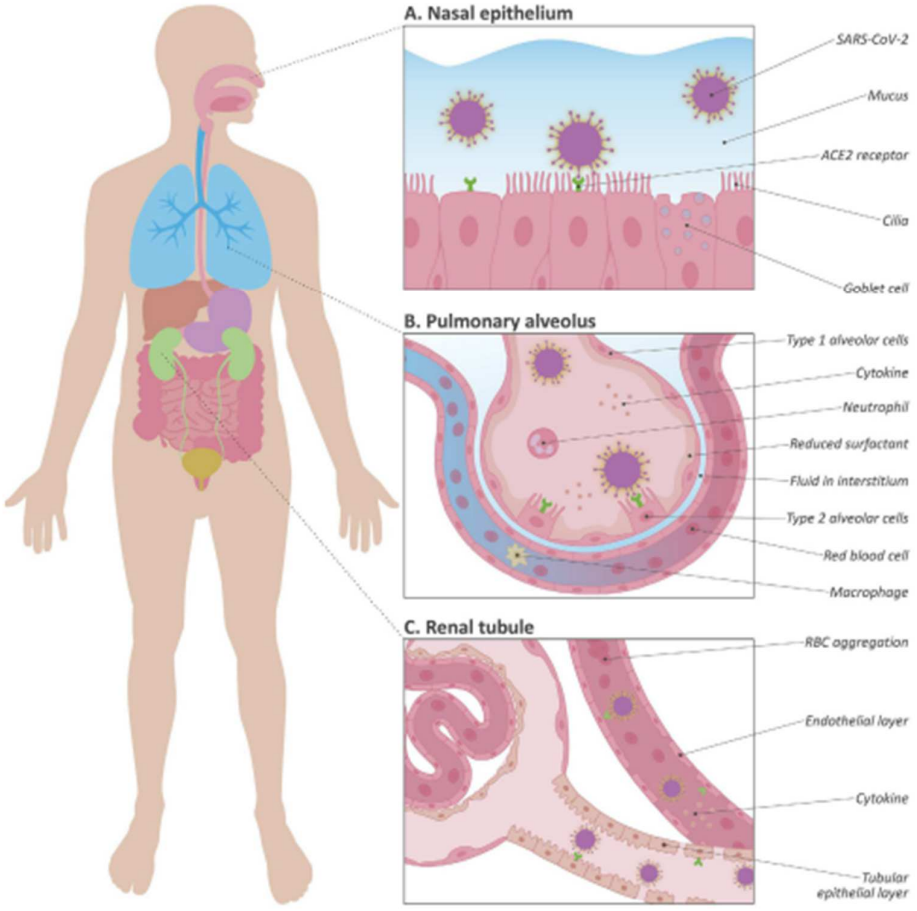

Figure-1 : Showing local ACE2 expression.

Figure 1 illustrates the role of ACE2 in the pathogenesis of COVID-19 disease (A–C). Figure A shows the attachment of SARS-CoV-2 virus to the ACE receptor on the mucosal membranes including nasal epithelia, which allows its entry into the human body. Figure B shows the invasion of respiratory epithelium and respiratory system by the SARS-CoV-2. Invasion of respiratory epithelium results in bilateral pulmonary oedema, diffuse reactive hyperplasia, alveolar septal thickening, and inflammatory infiltrates in the respiratory epithelium. Figure 3 shows the involvement of renal epithelium. Invasion of virus into renal epithelium results in tubular injury, changes in brush border cells, damage of capillary endothelial cells, RBC aggregation and occlusion of lumina.

Angiotensin Converting Enzyme (ACE):

The enzyme that changes angiotensin I into angiotensin II is called the angiotensin Converting Enzyme (ACE). Active vasoconstrictor angiotensin II tightens blood vessels and raises blood pressure. An easy blood test to gauge angiotensin levels is the angiotensin converting enzyme test. The test is typically requested to identify sarcoidosis, a granulomatous systemic illness that mostly affects the lungs. What is the purpose of the test? The test is important for determining whether sarcoidosis is present as well as for the diagnosis and follow-up of the condition. Leprosy and Gaucher disease may also be confirmed with the use of the test. The test is ordered when? If a person exhibits any of the following signs and symptoms of sarcoidosis, the test may be advised: breathing difficulty, persistent cough, large red eye, aching joints. The test may also be prescribed for those who are receiving therapy for sarcoidosis in order to track the disease's progression and evaluate how well the medication is working to manage the condition.

Exactly how is the sample taken?

An arm vein is used to draw blood for testing.

How can I get ready for the exam?

A doctor could recommend that a patient abstain from food and liquids for up to 12 hours before the ACE test. Additionally, it is preferable to check with the doctor about stopping any steroid medications if the patient is using them.[13]

Properties of Angiotensin 1-7:

Prolyl endopeptidase and NEP may produce angiotensin 1–7 directly from angiotensin I[14].The production of angiotensin 1-7 is mostly sourced from the heart, brain, and kidney[15]. NEP appears to have a more significant role in the synthesis of angiotensin 1-7 in the human coronary circulation than ACE2 [16]. Angiotensin 1-7 has a short half-life of 0.5 h in humans, according to pharmacokinetic studies [17].

ACE2 in human physiology:

ACE homologue, ACE2 regulates blood pressure and maintains electrolyte homeostasis as part of the renin-angiotensin-aldosterone system (RAAS) (Figure 2). Renin cleaves angiotensinogen, a substance generated by the liver, to create angiotensin I. (Ang I). Angiotensin I (Ang I) is converted to angiotensin II (Ang II) by a number of enzymes, including ACE[18]. The primary active RAAS component, Ang II, primarily affects angiotensin II type 1 receptors to produce its effects (AT1R). Some of the major side effects of Angiotensin II include, vasoconstriction, increased blood pressure, production of aldosterone, increased excretion of potassium and reabsorption of sodium into kidneys and increased inflammatory reaction[19,20]. Angiotensin (Ang II) is broken down by ACE2 to form angiotensins (1–7), which bind to the Mas receptor and have vasodilatory, anti-inflammatory, and anti-fibrotic actions[21]. Additionally, Ang I is broken down by ACE2 into angiotensin (1-9), which ACE then turns into angiotensin (1-7) [22], though this mechanism is typically of less

physiological significance. It is well known that ACE2 counteracts the effect of ACE. Therefore, the functional balance between ACE and ACE2 is essential to maintain the equilibrium between pro and anti-inflammatory/ anti-fibrotic pathways regulated by RAAS activation and subsequent angiotensin peptide release[22]. Numerous variables, including pharmaceutical RAAS blockage in a number of illness states, can influence this equilibrium. Several risk factors may result in imbalance in the ACE/ACE2 resulting in inflammation and fibrinogenesis. These risk factors include, increased dietary sodium, fat and fructose [23-26]. In addition to its role in the renin angiotensin system, ACE2 also controls the bradykinin metabolism in the lungs. It inactivates the desArg9 bradykinin ligand of bradykinin receptor type 1, thereby limiting the effects of bradykinin on vasodilation and increased vascular permeability [27]. ACE2 has been identified as a crucial regulator of the gut microbial ecology, local innate immunity, antimicrobial peptide production, and dietary amino acid balance in the gastrointestinal tract. In actuality, transplanting the intestinal microbiota of Ace2-knockout mice enhanced the risk of developing severe colitis [28]. Given that the respiratory and digestive systems both have interfaces with the outside environment, the high expression of ACE2 on pulmonary (alveolar epithelium) and intestinal epithelium are similar to the SARS-CoV-2 viral transmission pathways. In addition, ACE2 was found on smooth muscle cells and vascular endothelial cells in every organ examined. While weak ACE2 expression is noted in glomerular endothelial cells and mesangial cells, the ACE2 expression are moderate in the parietal epithelial cells and podocytes and significantly higher in the brush border of proximal tubular cells in the kidney. Additionally, ACE2is also observed in the oral and nasal mucosa as well as the basal epidermal layer of the epidermis. On the other hand, lymphoid organs and hepatobiliary system do not show ACE2 expression [26]. Strong evidence points to

RAAS-independent actions of ACE2 based on the high staining on a variety of epithelial cells in the body. Researchers are now interested in the role of ACE2 in viral transmission of COVID-19. Furthermore, regardless of the initial cause, increased expression of endothelial ACE2 is noted in the glomerular and interstitial capillaries during renal diseases, indicating ACE2 as a potential damage marker [29]. In conclusion, ACE2 is broadly expressed in human tissues, including the organs that SARS-CoV-2 targets as well as others that appear to be less crucial or even unrelated to the pathogenesis of COVID-19.

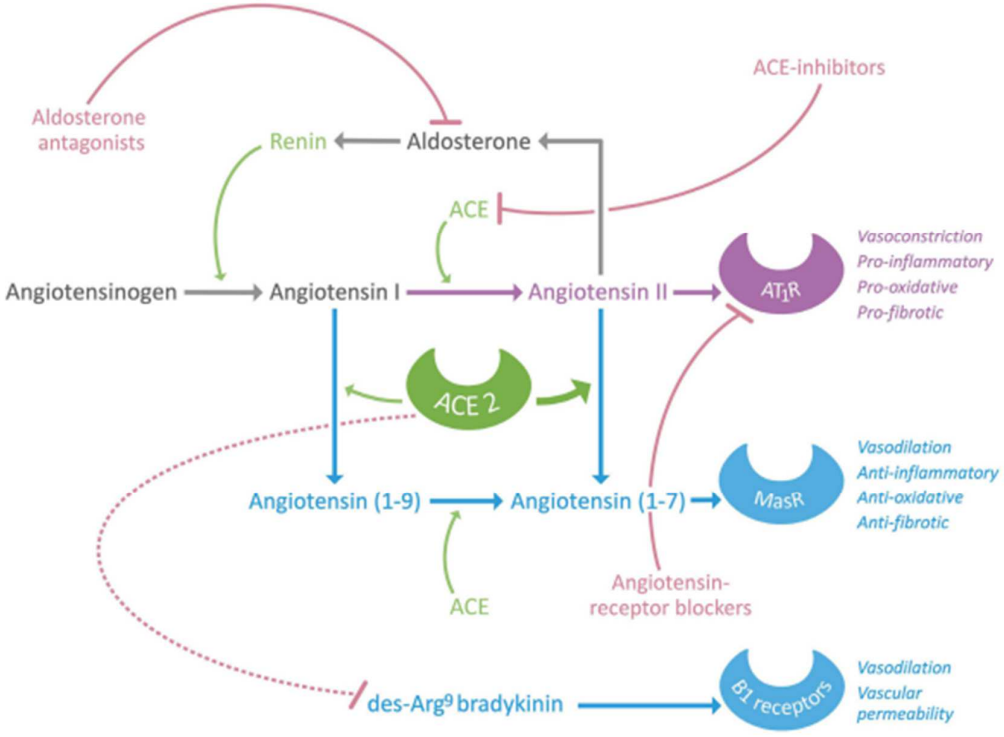

Figure-2: Correlation between ACE2 expression and organ damage

Interaction between ACE2 and SARS-CoV-2:

Recently, ACE2 was conclusively determined to be the SARS-CoV-2 functional host receptor (Figure 3).[8] SARS-CoV-2 virus have higher binding affinity of approximately 10 to 20 times than that of SARS-CoV-1 to the ACE receptors [8.9]. These findings may help to partially explain why SARS-CoV-2 seems to be more easily transmissible. They also suggest that higher ACE2 expression may make hosts more vulnerable to SARS-CoV-2 entrance. The spike protein present in the SARSCoV-1 attracts towards the ACE2 in the membrane epithelium and binds with ACE2 giving rise to further pathogenic events.[22,30]

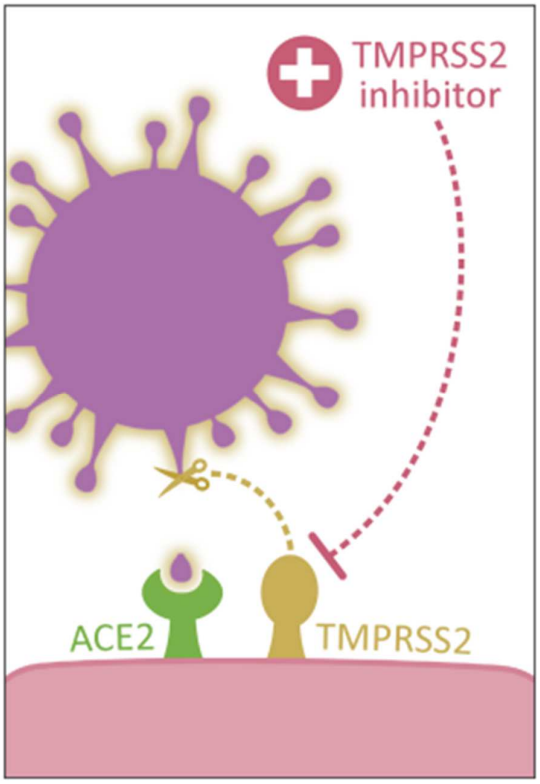

Figure-3: **As the host cell receptor**, ACE2 interacts with the SARS-CoV-2. Entry into the cell is dependent on the serine protease TMPRSS2 induced stimulation of viral spike (S) protein.

The significance of this receptor in the pathogenesis of SARS has been studied in an investigational preclinical study using Ace2-knockout mice [31]. The authors proposed that SARS-CoV-1 infection causes ACE2 to become internalised, which is caused by SARS-CoV-1 binding to ACE2, and that this process increases the severity of pulmonary diseases [31].This counteracts the presentive ability of ACE2 on disease progression resulting in severe disease characterized by ARDS. Additionally, Ang II's negative effects have already been proven in a number of ARDS animal models [32-35]. These results confirm the similarity between ACE2 driven host and viral interaction and subsequent events in both variants of CoV-2 virus.[8] During hypoxia, Ang II-induced pulmonary vasoconstriction takes place in an effort to correct the ventilation-perfusion mismatch, but it also has undesirable pro-fibrotic consequences that are both counteracted by concurrent ACE2 over expression [36]. Similar conditions might result in the downregulation of ACE2 caused by SARS-CoV-2, which would impede the removal of angiotensin 2, resulting in tissue damage. Alternatively, SARS-CoV-2 may also inhibit ACE2 in order to restrict viral dissemination by reducing the chance for further viral cell entrance. However, the possibility of COVID-19 infection is much higher in cells that express ACE2 which enables earlier and rapid viral entry and virus dissemination. However, the exact role of ACE2 function in the COVID-19 pathogenesis and infection is yet to be elucidated.

OBJECTIVES

- To study the serum angiotensin converting enzyme (ACE) levels as possible Biomarker in covid-19 patients and Prognostic implications.

REVIEW OF LITERATURE

Following the first pneumonia outbreak in Wuhan, China in December 2019, the virus now has spread rapidly across world. ACE 2 receptor present in the host epithelial cells is one of the crucial elements in the pathogenesis of CIVID-19 as it allows the entry of virus into the host cell. Several additional organs than the lungs are susceptible to the virus, according to our study of previously published SARS studies and more current research on SARS-CoV-2 illness, now known as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). The ACE2/angiotensin-(1-7) /MAS axis works to counterbalance the detrimental effects of the renin-angiotensin system (RAS), which is crucial for maintaining the physiological and pathophysiological balance of the body. ACE2 catalyses the conversion of angiotensin II to angiotensin-(1-7). The imbalance between the RAS and ACE2/angiotensin-(1-7)/MAS following infection and ACE2 downregulation, in addition to the direct impacts of the virus and the inflammatory and immunological processes linked to COVID-19 development, may potentially contribute to multiple organ harm. It is possible to create targeted medications, antibodies, and vaccinations against the spike protein of virus that specifically has affinity towards ACE2 receptor. Organ damage may be lessened by reestablishing the proper equilibrium between the RAS and ACE2/angiotensin-(1-7)/MAS. Similarly, the virus enters the lung tissue by binding to the ACE1 receptor in the pulmonary epithelium. Furthermore, the virus can conversely infect the ACE-2 expressing cells in various cells and organs, ultimately leading to multi-organ damage [37]. Interestingly, based on the preliminary epidemiological data, COVID-19 symptoms are relatively rare among children. In a cohort study, out of 44,672 diagnosed cases of COVID-19, only 1% patients belonged to the age of less than 10 years[38]. This might imply that kids are less prone to

infections or that infections in kids result in mild or silent illnesses that go mostly unnoticed. The SARS-CoV-2 virus, may enter cells more easily because its viral spike proteins link to ACE2 receptors on host membranes[39]. This suggests a positive correlation between patients with higher epithelial ACE2 receptor expression and susceptibility of COVID-19 infection [39]. However, a complex too much/too soon interaction is at work in this situation because it has been demonstrated that the related SARS-CoV virus down regulates ACE2 following cell entrance, a feature contributing to the severe lung diseases linked to this viral infection[40]. Reports suggest the inverse actions between ACE and ACE2 in the RAS. Drugs that block ACE action, for instance, cause the expression of ACE2. As a result, low levels of ACE2 and high levels of ACE may be related[41]. Children's serum ACE volumes are greater than adults'[42]. Could this discrepancy be explained by a lower level of ACE2 expression in children than in adults, given the opposing effect of ACE and ACE2? While studies have reported that pediatric and adolescents comprise of only 1% of the entire study cohort in a Chinese population[38], another study has reported significantly higher amounts if circulating ACE among teenagers as compared to adult population[42]. The lower amount of membrane bound ACE2 among teenagers and children may explain the lower prevalence of symptomatic COVID-19 among these population. However, this is yet to be validated. The relationship between serum ACE and ACE2 expression in tissues like the airway epithelium and other tissues is also not known. Therefore, the ability of the data to make a connection between the aforementioned hypotheses is crucial to the concept that serum ACE can be considered an indicator of the COVID-19 severity. While low circulating ACE indicates mild illness, high levels indicate severe illness [40]. Therefore, this biomarker may be beneficial especially in the early identification of patients reporting to the

hospital and categorizing them based on severity. Furthermore, it aids in better management of patients from diagnosis to outcomes.

Angiotensin-converting enzyme 2 (ACE2), the primary receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is expressed on the surface of endothelial cells [43, 44]. Previous studies have reported the beneficial effect of intravenous recombinant ACE2 therapy in the prevention of the viral entrance into the target cells, as an effective treatment in severe COVID-19 patients[45]. Endothelial cells infected with SARS-CoV-2 are encouraged to become infected by ACE2, which causes endothelial activation, damage, and a significant release of factor Xa from Weibel-Palade bodies. And increased levels of vascular adhesion molecule-1 [46, 47]. Furthermore, there is an imbalance in the RAAS system among COVID-19 patients which is characterized by increased levels of ACE2, renin, and kallikrein enzymes [48]. However, it is unclear how the interactions between the aforementioned factors affect the clinical result. Another study has described a patient with critically ill COVID-19 diagnosis with concurrent ARDS who showed improvement in symptoms upon treatment tocilizumab, corticosteroids, immunoglobulin, and antimicrobials. The patient was monitored based on levels of circulating ACE2 and soluble adhesion markers. Mortality is predicted by serum ACE2 activity and corresponds with COVID-19 severity.

ACE2 is one of the vital enzyme in the RAS, it binds to a variety of substrates including ghrelin, apelin-13, neurotensin-1-11, dynorphin A-1-13, angiotensin I, and angiotensin II[49]. Glycoprotein S (homotrimer) on the surface of SARS-CoV-2 interacts with ACE2 receptors[50, 51]. The SARS-CoV-2 protein S's primary receptor for attaching to host cells has been identified as ACE2. Previous research have also suggested that extracellular matrix metalloproteinases, sialic acid receptors and

transmembrane serine protease 2 may also potentially facilitate virus entry[52, 53]. The spoke protein subunits S1 and S2 of the SARS-CoV-2 virus present at the N -terminus are main components of viral adhesion to the host cells. At the host and virus interface there is fusion of S1 subunit with peptidase of ACE2 receptor and S2 subunit will further facilitate the fusion of virus and host cells and entry of viral genome[51],[54]. Further cleavage and dissociation of spike protein by the protease enzymes of host will result in spread of infection [51]. Main proteases involved in the dissociation of spoke protein include type II transmembrane serine proteases, HAT, catepsin B and L, elastase, trypsin, and furin. Following dissociation, and cleavage of SI and S2 proteins, the hydrophobic fusion peptide is released into host cell membrane.[55, 56] Sequence homology investigations reported numerous aminoacid replacements in the RBD of SARS-CoV-2 protein S as compared to SARS-CoV, thereby increasing its affinity for ACE2 and fortifying its connections with other proteins. The interaction site in SARS-CoV-2 virus is much larger than SARS-CoV, is comprised of 21 vs 17 aminoacids, which increases the chance of more direct contact with ACE2 receptor[57,59]. According to Shang et al., unlike SARS-CoV, SARS-CoV-2 causes protein S pre-activation by proprotein convertase furin, which increases RBD's affinity for ACE2. This promotes effective viral entrance into the host cells and makes it easier for the virus to evade the immune system. The authors made the following hypotheses: [57, 58]. This is the cause of the high rate of viral transmission. Briefly, upon binding of the SARS-CoV-2 to ACE1 receptor, there is interaction between fusion peptide present in S2 spoke protein of virus and lipid layers of the host cell. This further results in fusion of membranes, forming endosomes, where the cysteine proteases cathepsin B and L and the serine protease TMPRSS2 cleave protein S and facilitate the release on how the proteases cut the spike protein, however, there is still

much to learn. In contrast to SARS-CoV, SARS-S1/S2 CoV-2's cleavage site has an extra RRAR motif, as demonstrated by Xia et al.

The motif is mainly a furin cleavage site (FCS), which are broken down by enzymes to promote viral infection and dissemination [61,62]. [51, 58] demonstrated that the host cell membrane serine protease TMPRSS2 may activate the SARS-CoV-2 spike protein enabling the virus entry into the host cells by endosome formation. Previous study has reported that the endosome formation and endocytosis proves is pH dependent and occurs only at acidic pH of 3. Cathepsin B and L gets activated by the acidic pH pf the lysosome and endosomes, further enabling the cleavage of spike protein of virus into its subunits. The subunit S2 is utilised for membrane fusion whereas S1 binds to ACE-2[63]. Numerous characteristics of SARS-CoV-2 pathogenesis can be explained by the involvement of a number of proteases in the virus-ACE2 interaction. These mechanisms have been shown in the previous researches. Inhibition of TMPRSS2 serine protease by camostat mesylate prevented the incidence of SARS-CoV-2 infection of lung cells as shown by [51].This study concluded that TMPRSS2 is necessary for the viral spike protein to be primed for cell entry. Subsequent studies showed that inhibition of cathepsin L and B and TMPRSS2 by E-64d and camostat mesylate, respectively will facilitate complete suppression of viral infection. Furthermore, ammonium chloride also is beneficial in blocking cathepsin L and B cysteine proteases[51]. Viral RNA polymerase in cells causes virus amplification leading to disease and viral spread. Organ malfunction and accelerated infection propagation might result from this. Due to the presence of bilayer vesicles in the virus and suppression of the Receptor Recognition Pattern, the immune system fails to recognize the voral particles [63-65]. In a manner similar to how SARS-CoV down regulates ACE2 expression, the viral entry if dependent on ACE-2 receptor [66-

[69]. Furthermore, the sialic acid present in the glycoproteins of host cells act as hemagglutinin esterase receptor for the virus. The viral entrance is facilitated by HE's binding to sialic acid moieties. The entrance of SARS-CoV-2 appears to require HE-mediated fusion of the virus and host cell membrane [70, 71]. The well-known receptor for SARS-CoV-2 entrance is ACE2 [72]. The reaction's equilibrium is altered by ACE2 dysregulation. As a result, the concentrations of ACE2's products fall while its substrates increase. This may aggravate the disease's pathophysiology and cause mortality.

ACE2:

ACE2 consists of 2 main domains, the N terminal present extracellularly and C terminal present intracellularly. The binding of virus spike protein and ACE2 will trigger subsequent processes resulting in internalization of the virus[73]. ACE2 is predominantly expressed on the smooth muscle cells, cardiac muscle cells, fibroblasts, endothelium, renal cells, hepatic cells, intestinal epithelium, testes, brain, pulmonary epithelium and oral mucosa [74-78]. Although ACE2 is a transmembrane protein, COVID-19 patients' plasma contains a small amount of soluble ACE2 [79]. ACE2 is mostly found on the apical cell surface as opposed to the basolateral and apical locations of ACE [80]. ACE2 has 42 percent sequence similarity to ACE (EC 3.4.15.1). The major difference between ACE2 and CACE is that the former is a mono-carboxypeptidase and the latter is dipeptidyl-carboxypeptidase [81,82]. The enzyme consists of a signal peptide, transmembrane domain, and zinc binding active site. Vasoactive peptides are present at the catalytic site [81]. Despite having comparable structures, ACE-2 is not inhibited by ACE inhibitory antibodies[81,82]. Patients using ACE inhibitory antibodies, however, had elevated levels of ACE2[83, 84]. ACE2 cleaves Apelin (1-13), dynorphin A (1-13) and casomorphin (1-7) to apelin

(1-12), to dynorphin (1-12), and to - casomorphin (1-6), respectively [2]. Similarly, Angiotensin 2 and angiotensin 1 are converted to angiotensin (1-7) and angiotensin (1-9), respectively. A putative renin-angiotensin system regulator is ACE2 (RAS). Moreover, combination of ACE2 and virus results in impairment of RAS and increase the risk of disease severity including incidence of acute respiratory symptoms [85]. Additionally, severity of CIVID-19 is also related to decreased expression of ACE2 due to SARS-CoV-2 infection as an inverse mechanism[68]. Here by we will discuss more in detail about the substrates and products if ACE2 to better undertsnad the pathophysiology of COVID -19 and its relationship with ACE2 receptors.

Ang II:

Renin, which is secreted from kidney juxtaglomerular cells, acts on angiotensinogen to create angiotensin I[86]. The catalytic activity of ACE transforms Ang I into Ang II, especially in various epithelium across organs including lungs, kidney, brain and heart. Previous study using a rat model has shown that angiotensin II is converted to either Angiotensin (1-7) or Angiotensin III by ACE2 or angiotensinases, respectively [87], both of which have half-lives of around 16 s in plasma [88]. Angiotensin II is an active octapeptide, which upon binding with AT-1, AT-2, and AT-4 receptors activates the physiological actions (Fig. 1)[89]. The main roles of Ang II secondary to its avtivation by AT1 are vasocontraction [90], inotropy [91], sympathetic nervous system augmentation [92], diffusion of vasopressin, peripheral sympathetic nervous system and pituitary organ modulation, and regulation of aldosterone production[90,93]. Although AT-2 receptors are present across emberyonic organs, their expression is mostly found in the ovary, brain, kidney, and vascular endothelial cells, which operate as vasodilators by secreting bradykinin and nitric oxide[94].

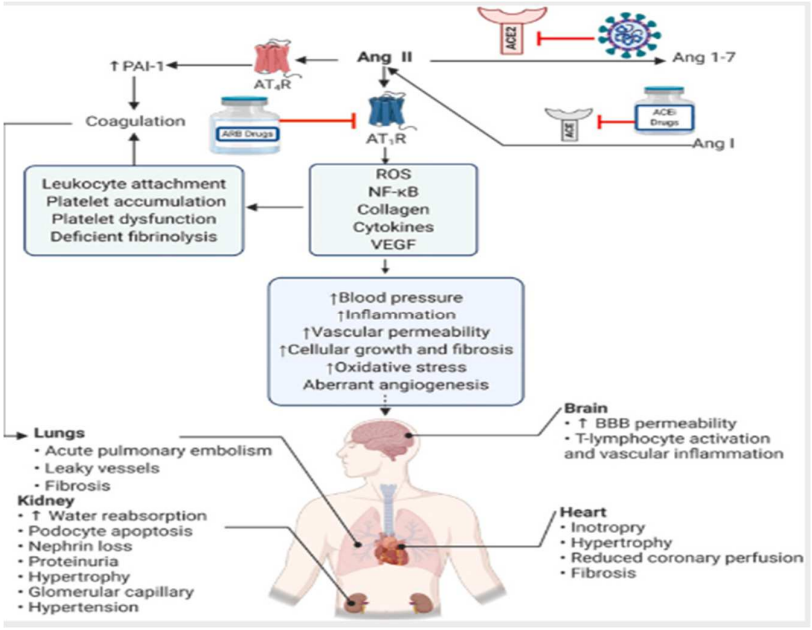

Figure-4: Effects of Ang II on organs

Effects of Ang II on different organs

As previously discussed, Ang II is formed by conversion of Ang I to II by ACE, Ang II is further converted to Ang 1-7 by ACE2 receptors. Excessive conversion of Ang I to ang II results in accumulation of Ang II. This results in feedback mechanism wherein the SARS-CoV-2 downregulated the expression of ACE2 thereby increasing the severity of COVID-19 resulting in dissemination of the infection and multiorgan involvement. Angiotensin converting enzyme, angiotensin 1–7, and angiotensin–converting enzyme–2 Angiotensin II receptor type 1 is known as AT1R, whereas type 4 is known as AT4R. REACTIVE OXYGEN SPECIES: Plasminogen Activator Inhibitor-1, Vascular endothelial growth factor (VEGF), Blood-brain barrier; ARB medications: angiotensin II receptor blocker; ACEi medications: angiotensin-converting enzyme inhibitors.

Patients with COVID-19 experience a rise in angiopoietin-2 during acute respiratory distress syndrome (ARDS)[95]. The elevated angiopoietin-2 to angiopoietin-1 ratio in ARDS patients is consistent with this. Angiopoetin-2

overexpression may indicate a lethal outcome [96]. In patients with acute pulmonary damage, Ang II plays a critical role in enhancing vascular permeability by upregulating angiopoietin-2, angioprotein-2, and VEGF production[97]. Elevated VEGF expression secondary to hypoxia is predominant in ARDs patients which results in increased vascular permeability [98]. and inflammatory reactions were triggered by focal adhesion tyrosine kinase (FAK)[99]. Previous preclinical studies using mouse models have shown the ability of angioprotein-2 in causing epithelial necrosis, inflammation and cellular death secondary to hypoxia. The plasma concentration of Ang II and the severity of COVID-19 are correlated, according to a recent research in non-hypertensive human subjects [100]. Since it controls ACE2's activity adversely and affects angiogenesis, oxidative stress, hypertension, and other conditions that can build up and make COVID-19 more severe.

Ang (1-7):

Ang II is primarily reduced to Ang (1-7) by ACE2 and to some extent by Prolyloligopeptidases and prolyl carboxypeptidase, these enzymes remove the C-terminal phenylalanine from Ang II, [33]. Ang (1–7) is a physiologically active peptide that inhibits inflammation, angiogenesis, and vasocontraction by binding to the MAS receptor (Fig. 5) [101, 102]. The activation of Ang 1–7 takes place through its receptors (MasR). In COVID-19 patients, the virus downregulates the ACE2, which results in lower levels of Ang (1-7), thereby decreasing ots physiologic functions. (Created in BioRender.com). Ang (1-7) has anti-inflammatory, anti-hypertensive, and stimulatory effects on clot formation, which may be beneficial in COVID-19 patients to prevent thrombosis.

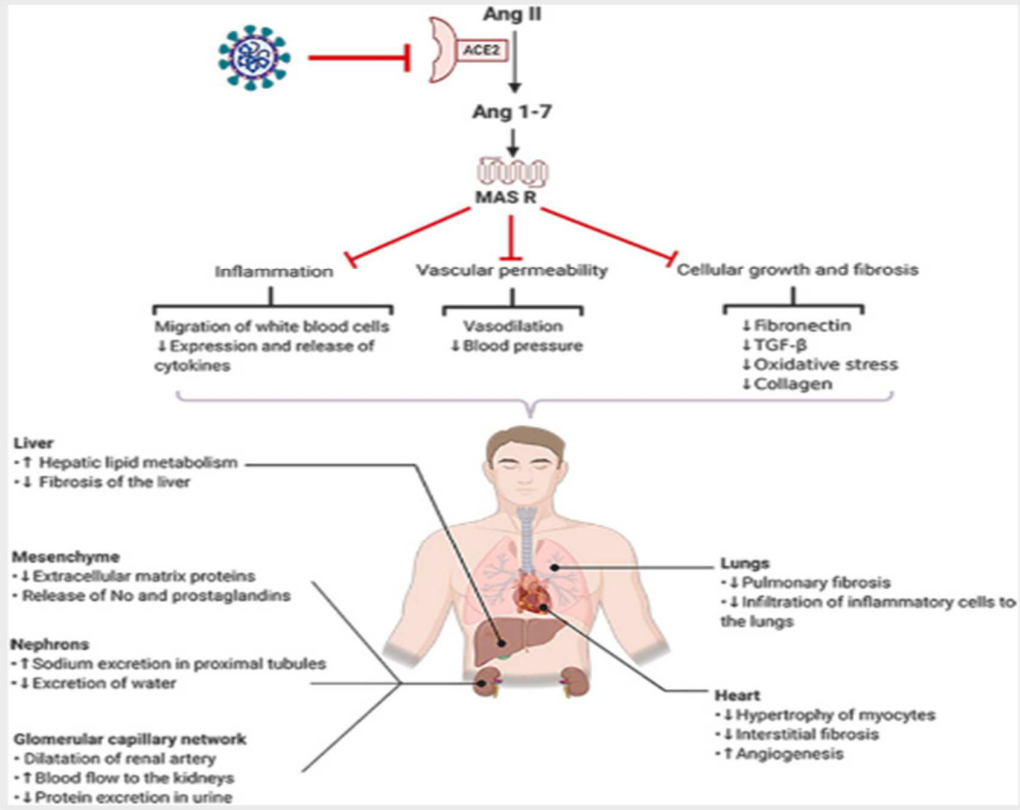

Figure-5: Ang 1–7 functions in several organs.

Ang (1-9):

Ang II is converted to Ang (1-9) mainly through ACE2 or catepsin A [103]. Ang (1–9) binds to AT2R and inhibits Ang II–AT1R signalling axis and further regulates the vasoconstriction, vasodilatory and antiproliferative axis [104] and so improving cardiovascular conditions [105]. The main activities of the AT2R-derived signalling include, Cell differentiation, vasodilation. It also decreases cell proliferation, has anti-inflammatory and antifibrosis effect [106]. Endothelial cells are affected by Ang (1–9), which lowers blood pressure [107].

In an invitro experimental model of human heart, endothelial repair of the atrial and ventricular tissues were driven by the release of NO and arachidonic acid by the endothelial cells which increased bradykinin levels [108]. Additionally, Ang (1-9) reduces the fibrosis of tissues, particularly in the cardiac and pulmonary tissues [104, 109]. As CIVID-19 is predominantly a respiratory pathogen and is associated with severe pulmonary fibrosis, Ang (1-9) can be used as therapeutic to counteract the pulmonary fibrosis. As a result, it is expected that Ang (1-9) works in concert with Ang (1-7) to reduce inflammation in COVID-19 patients. Downregulation of ACE2 is responsible for the difficulties caused by low levels of Ang (1–9). (Fig. 6).

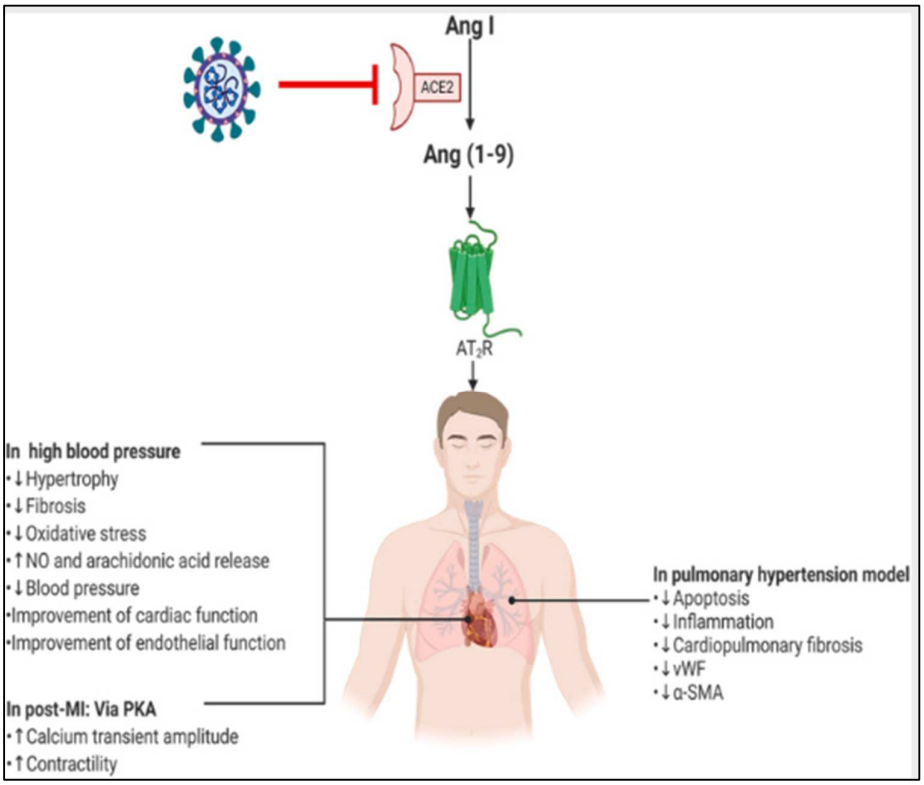

Figure-6: Ang 1–9 functions in human organs.

Briefly, conversion of Ang 1 to Ang (1-9) is mainly driven by ACE2. The Ang (1-9) through its receptor AT2R activates various changes in the body. During COVID-19, as the virus downregulates the expression of ACE2, the Ang (1-9) levels in the body are substantially low. Patients with COVID-19 lose the therapeutic effects of Ang 1-9 in various organs due to a drop in its concentration. Angiotensin converting enzyme type 2, angiotensin I, angiotensin I-9, AT2R, angiotensin II receptor type 2, von Willebrand factor, myocardial infarction, and -SMA are all abbreviations for the same compound.[110]

Immune responses and the renin-angiotensin system are related (RAS):

SARS-CoV-2 is mostly prevented by innate and acquired immunity, although the virus can also cause cytokine storms or hyperinflammation[111]. Although several variables cause cytokine storms, it may be interesting to investigate how the immune system is affected by ACE2 dysregulation (Fig.7). According to a previously published study, individuals with COVID-19 who have ACE2 downregulation in their macrophages produce more inflammatory cytokines and NO. On the other hand, Ang II promotes the growth of cells and the generation of cytokines, suggesting that it controls cell signalling in inflammatory and immune-related illnesses [112]. An immune molecule called IL-2 promotes the growth of T cells[113].

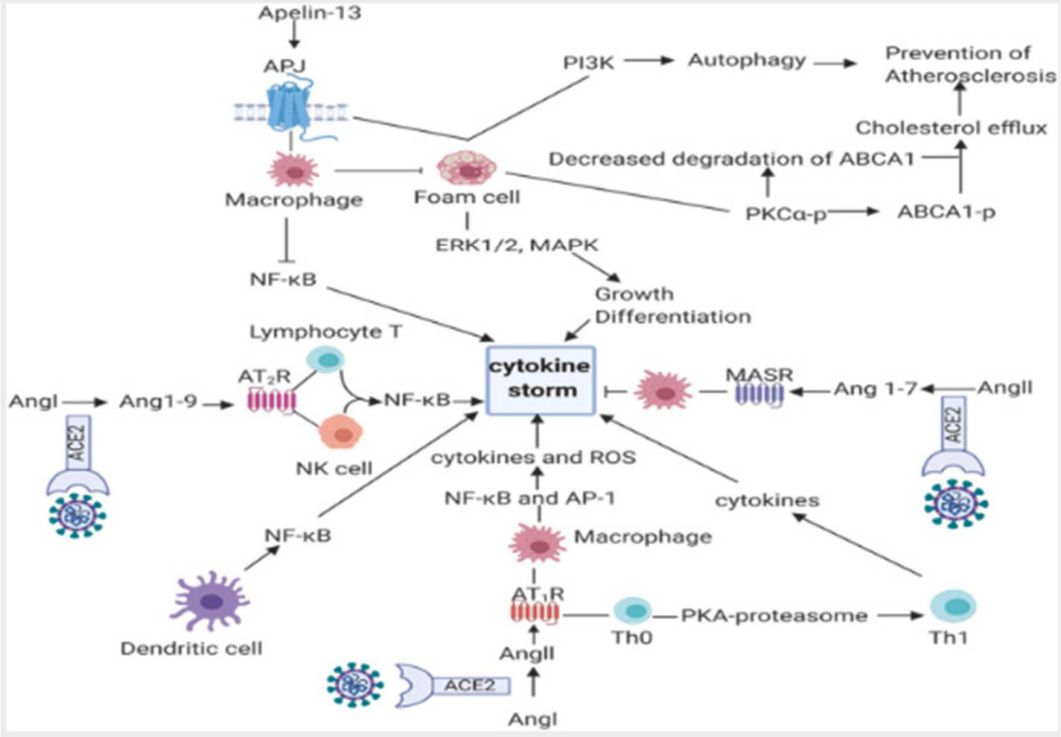

Figure-7: Schematic representation of immune system interactions with ACE2 substrates and products

Abbreviations: ACE2, Angiotensin converting enzyme 2; Ang (1-7), Angiotensin 1-7; AT1R, Angiotensin II receptor type 1; AT2R, Angiotensin II receptor type 2; Ang I, Angiotensin I; Ang II, Angiotensin II; Ang (1-9), Angiotensin 1-9; MAS R, Mas receptor; APJ, Apelin receptor; ROS, reactive oxygen species; ERK1/2, Extracellular signal-regulated kinases 1/2; MAPK, Mitogen-activated protein kinase; PI3K, Phosphatidylinositol-3-Kinase; PKC, Protein kinase C; Th1, T helper cell 1; Th0, naive T cell; NF-B, Nuclear factor-B; AP-1, Activator protein 1; ABCA1-p, Phosphorylated ATP binding cassette transporter A1.

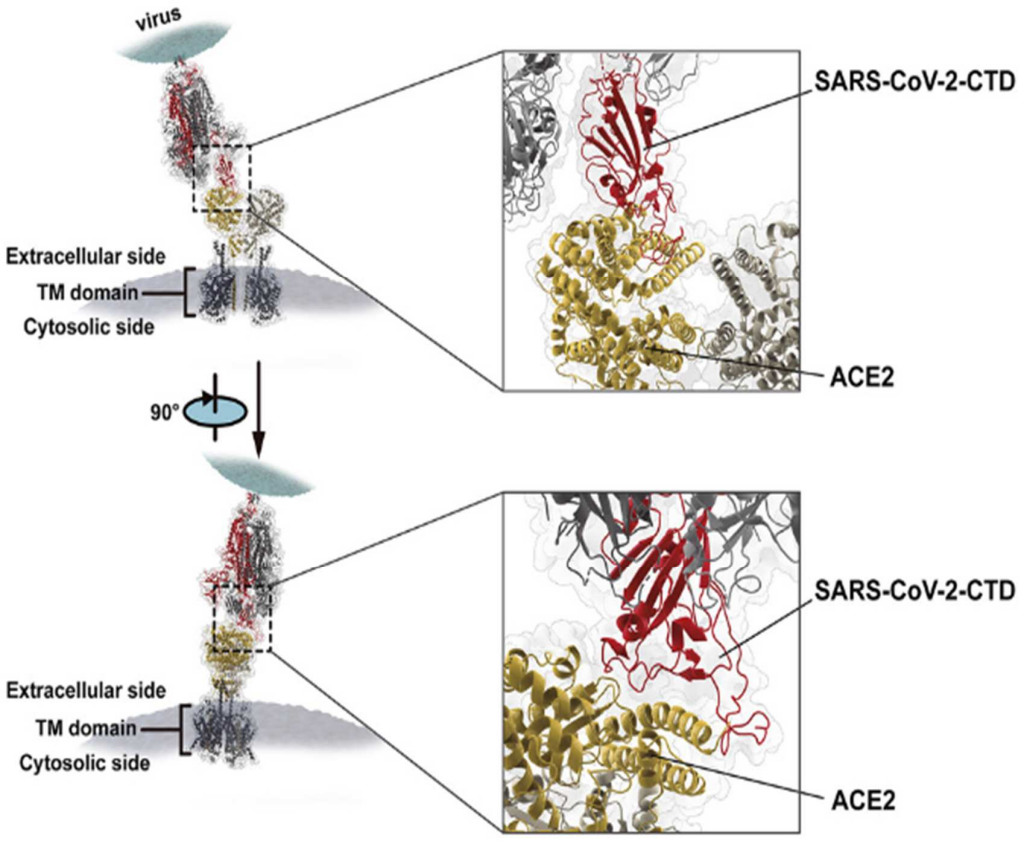

Figure-8: Molecular structure of ACE2 and SARS-Cov-2

Potential disease severity biomarkers include ACE2, serum ACE in COVID19:

According to preliminary epidemiological data symptomatic COVID-19 is very rare among children. In a COVID-19 epidemiologic study among 44,672 Chinese patients, only 1% patients belonged to the age group of <10 years [100]. This might imply that kids are less prone to infections or that infections in kids result in mild or silent illnesses that go mostly unnoticed. The SARS-CoV-2 virus enters cells more easily because its viral spike proteins link to ACE2 receptors on host membranes [39]. These findings suggest a positive relationship between ACE2 expression and COVID-19 infection susceptibility [39]. However, a complex too much/too soon interaction is at work in this situation because it has been demonstrated that the related SARS-CoV virus downregulates ACE2 following cell entrance, a feature contributing to the severe lung diseases linked to this viral infection[40]. It is believed that ACE and ACE2 have counter-regulatory interactions in the RAS as they participate in the opposing axis of RAS. Drugs that block ACE action, for instance, cause the expression of ACE2 [41]. As a result, low levels of ACE2 and high levels of ACE may be related [41]. Children's serum ACE volumes are greater than adults' [42]. This could be related to the lower level of lower level of ACE2 expression in children than in adults, suggesting the counter activities of ACE and ACE2. As shown previously, in a large Chinese cohort, symptomatic COVID 19 children comprised only 1% of the total population [38]. Furthermore, another study reported that which supports serum ACE levels are more in teenagers as compared to adults [42]. However, the relationship between membrane bound ACE2 and lower prevalence of symptoms in COVID-19 among children is yet to be elucidated. The relationship between serum ACE and ACE2 expression in tissues like the airway epithelium and other tissues is also not known. Another study has established a

positive relationship between ACE2 and severity of COVID-19. While mild cases had low serum ACE levels, high serum ACE levels were indicative of severe disease[40]. Therefore, the ability of the data to make a connection between the aforementioned hypotheses is crucial to establish serum ACE as an effective biomarker of the diagnosis and severity of COVID-19. This may further aid in categorizing the patients based on severity and subsequent management approaches specific to disease severity.

Early triage of critically ill COVID-19 patients: Potential role of Biomarker

Biomarker is defined as any characteristic or component which can be tested which will indicate and differentiate the normal physiologic and pathologic process in the body. Biomarkers are beneficial in identifying the risk of disease, disease severity, progression and outcome of the disease. The benefits of using COVID-19 biomarkers are as follows:

- Early diagnosis
- Categorization of disease based on severity
- formulation of hospital admission standards
- identification of high risk cohort
- ICU admission standards formulation
- Therapy justification
- Therapy response evaluation
- Outcome prediction, and
- establishing standards for ICU and/or hospital release

For discovery pf possible biomarkers, the in-depth knowledge of the pathophysiology of COVID-19 disease is paramount. The COVID-19 illness spectrum is varied, and age and the existence of co-morbid conditions affect how the disease manifests. Early suspicion, diagnosis, monitoring, and detection of problems, as well as patient care and disposition, all depend heavily on biomarkers. Each of these elements alone may have significant effects on the administrative structure and the healthcare system, directly affecting patient care. It goes without saying that clinical assessment will be crucial at every stage, and bedside decision-making will need to significantly include biomarkers. Instead of using a single biomarker, you could choose to use a biomarker panel. You cannot disregard difficulties with availability and price. The large amount of data that is constantly being added to the COVID-19 literature makes it hard for doctors to compile and critically analyse it in order to extract information that is practically beneficial for patients. It is crucial to have national or regional policies that adapt the information accessible to the needs of the local community[114].

Previous studies:

Butler-Laporte et al., 2021 [115] conducted a post hoc analysis of 2 studies to assess the genomic relationship between ACE levels in COVID-19 patients. The ORIGIN study included 4147 patients and GWAS study included 960.186 patients. Among these cohorts, between 18 and 37 percent of the variation in ACE levels can be attributed to genetic variations. In the ORIGIN and GWAS studies, hospitalization, severe illness did not have effect on genetic susceptibility of ACE levels in COVID 19 patients. The outcomes of many sensitivity studies were comparable. The susceptibility to or severity of COVID-19 illness were not related to genetically reduced serum ACE levels. These findings imply that people taking ACE inhibitors

shouldn't stop their medication during the COVID-19 epidemic. The authors concluded that genetic polymorphisms highly related with ACE levels that were close to the ACE gene.

In a study by **Wang et al., 2020,** [116]138 hospitalized NCIP patients were evaluated. The median age of the patients was 56 years and 54% were men. Hospitalized patients (29%) and afflicted healthcare workers (29%) were suspected of contracting the virus through hospital-associated transmission (12.3%). Most common reported symptoms were fever (99%), tiredness (70%), and dry cough (59%). The reported laboratory changes were as follows: Eighty patients had prolonged median prothrombin time of 13 seconds, 55 patients had elevated median LDH levels of 261 U/L and 97 patients had lymphopenia. On computed tomography examination, all patients had bilateral patchy appearance resembling ground glass opacity suggestive of COVID-19. Most common treatment regimens included oseltamivir, antimicrobial therapy and glucocorticoid therapy. Frequency of Severe COVID-19 cases requiring ICU treatment was 26%. Common reasons for ICU admission were ARDS, arrhythmia and shock. The median time from onset of symptoms to dyspnea, hospitalization and ICU admission were 5, 7 and 8 days, respectively. Compared to the - patients, ICU admitted patients were older, had underlying comorbidities and severe symptoms including dyspnea and anorexia. Among ICU admitted patients, 17 patients needed invasive ventilation, 15 patients required non-invasive ventilation while 4 patients were treated with high flow oxygen.

Whereas, **[Liang et al.,2020],** [118]concluded that, it is quite concerning that individuals with the new coronavirus disease of 2019 (COVID-19) have suddenly deteriorated into serious illness. Early detection of these patients is essential. We demonstrate that based on clinical variables upon admission, a deep learning-based

survival model can predict the likelihood that COVID-19 patients would experience a critical illness. We produce this model, employing a dataset of 1590 patients from 575 medical facilities and a concordance index of 0.894 for internal validation. Using three different cohorts, we further verify the model. Consisting of 1393 patients with concordance from the provinces of Wuhan, Hubei, and Guangdong 0.890, 0.852, and 0.967, correspondingly, indices. This model is used to develop an online tool for calculation that is intended for patient triage at admission in order to identify patients at risk of severe illness, ensuring that patients at greatest risk of severe illness receive appropriate care as soon as possible, and enabling effective allocation of healthcare resources.

[Zhu et al.,2020], [119] said that, the 16 severe patients out of the 136 individuals with confirmed COVID-19 were older, had a higher body mass index (BMI), and had a greater percentage of hypertension than the 120 nonsevere patients. The baseline serum ACE activity of participants in the severe group and non-severe group were lower than those of normal controls, with the severe group having the lowest level. There were no appreciable changes between the severe group, nonsevere group, or normal control group throughout the recovery period, however the serum ACE activity rose during this time. Since low serum ACE activity was related with the severity of COVID-19 at baseline and the activity rose with the illness's remission, it might be employed as a marker to represent the clinical status of the disease.

Kragstrup et al., 2021 [120] conducted a larger longitudinal study with data from MGH Emergency Department. The study was divided into COVID 19 positive and negative cohorts with 306 and 78 patients, respectively. Following baseline data collection, patients were prospectively followed up for 28 days to evaluate the COVID-19 outcome. Olink® Explore 1536 platform was used to quantify the ACE2

protein levels. Patients with elevated plasma ACE2 levels had higher odds of severe disease in 28 days (OR [95% CI]: 1.8[1.4-2.3]; p=0.0001). ACE2 levels were significantly higher among COVID-19 patients with preexisting hypertension (p=0.0045), patients with renal disease (p=0.0363) and cardiac disorders (p=0.0303) as compared to COVID-19 patients without comorbidities. The authors concluded that plasma ACE2 levels will be beneficial in predicting COVID-19 outcome. Furthermore, ACE2 levels are significantly correlated with comorbidities and COVID-19 outcome.

In another study done by **[Chen et al., 2021]**,[121]120 patients with confirmed COVID-19 who underwent serum ACE detection upon entry were retrospectively included. During hospitalisation, clinical traits and laboratory results were dynamically assessed to uncover possible risk factors for illness development. It was shown that one of the independent risk variables is ACE level. In comparison to patients with ACE level [33.5 U/L, those with ACE level B 33.5 U/L displayed greater cumulative viral RNA detection rates, raised levels of pro-inflammatory mediators, lower lymphocyte counts, and decreased SARS-CoV-2-specific antibodies. The development of COVID-19 is influenced by lower serum ACE levels in connection to delayed virus eradication, hyperinflammation, and reduced host antiviral immune responses.

Fagyas et al., 2022 [122] conducted a study to comparatively evaluate the relationship between ACE2, inflammatory biomarkers and comorbidities with clinical outcome among patients with severe sepsis with or without COVID-19. Baseline ACE2 activity was significantly higher amon critically ill COVID 19 patients as compared to severe COVID 19 patients and COVID-19 negative patients (54 mU/L vs 35 mU/L vs 41 mU/L; p-0.0260). These results were independent of comorbidities. Among

critically ill patients, there was a positive relationship between serum ACE2 levels with inflammatory biomarkers. At an AUC of 0.7, baseline ACE2 levels were considered an independent predictor of COVID-19 severity ($p<0.0001$). At the time of hospitalization, non-survivors had greater serum ACE2 activity than survivors ($P< 0.0001$). Furthermore, increased ACE2 activity (45.4 mU/L) indicated a greater risk for 30-day mortality (65 vs. 37 %; $p<0.0001$). The authors concluded that baseline Serum ACE2 levels predict the COVID-19 severity and outcome in COVID-19 patients.

MATERIALS AND METHODS

Study design-A Cross-Sectional study

Study period- 1st October 2020 to 31st September 2021

Sample size- 101`

Calculated using formula

Formula used for sample size calculation is,

$$n = \frac{p\,(100 - p)Z^2}{E^2}$$

where n is the sample size required, p is the percentage occurrence of a state or condition (proportion or prevalence), E is the percentage maximum error required, Z is the value corresponding to level of confidence required.

The hospital-based prevalence was observed to be 73%. Considering this at 95% confidence level and 12% of prevalence as maximum error (i.e., E=8.76), the sample size is given by,

$$n = \frac{73 \text{ x } (100 - 73) \text{ x } 1.96^2}{8.76^2}$$

$$n = 98.67123 \approx 99$$

Hence, the minimum sample size required is 99. As sample size increases, accuracy of result also increases. Here, sample size is taken to be 101.

Inclusion criteria

All covid-19 adult patients > 18 years of age coming to casualty with RT-PCR positive status and / or Rapid Antigen Test positive.

Exclusion criteria

- Hyperthyroidism
- Hypothyroidism
- Miliary tuberculosis
- Asthma
- COPD
- Sarcoidosis
- Chronic liver disease

Methodology

- Patients admitted in KLES hospital fulfilling provisional diagnosis of covid-19 infection were included in the study.
- Informed consent was obtained.
- Institutional ethical clearance was obtained.
- A detailed history, clinical findings were noted.
- Samples are processed in spectrophotometry- enzymatic (substrate fapgg)
- Other relevant investigations like Complete Blood Count, Mini Renal, LFT, D-DIMER, Ferritin, CRP, LDH, IL-6 levels HRCT thorax (CT severity score) etc. were recorded.
- Clinical improvement of patient will be observed and results was formulated.
- Data was analyzed and tabulated.

STATISTICAL METHODS

Data is analysed using statistical software R version 4.2.1 and Microsoft Excel. Categorical variables given in the form of frequency tables. Continuous variables given in Mean ± SD / Median (Min, Max) form. Chi square test is used check the association between categorical variables. Normality of variable is checked by Shapiro Wilk test and QQ plot. Two sample t test is used to compare means of variables over outcome. Mann Whitney U test is used to compare the distribution of variables over outcome. Applicability of serum ace levels to predict outcome is checked by Logistic regression. Kruskal Wallis test is used to compare the distribution of variables over CT severity score. Spearman's rank correlation test is used to check the correlation of different variables with serum ace levels. P-value less than or equal to 0.05 indicates statistical significance.

.

RESULTS

Data contains measurement on 101 subjects whose age ranges from 19 to 88 years with mean age of 52.28 ± 14.55 years. The gender ratio is 2.16:1. The following table gives the distribution of subjects according to outcome.

Table 1: Distribution of subjects according to outcome.

Outcome	Number of subjects (%)
Expired	15 (14.85%)
Improved	86 (85.15%)

Out of 101 subjects with COVID, improvement was observed in 86 (85.15%) subjects while 15 (14.85%) subjects expired.

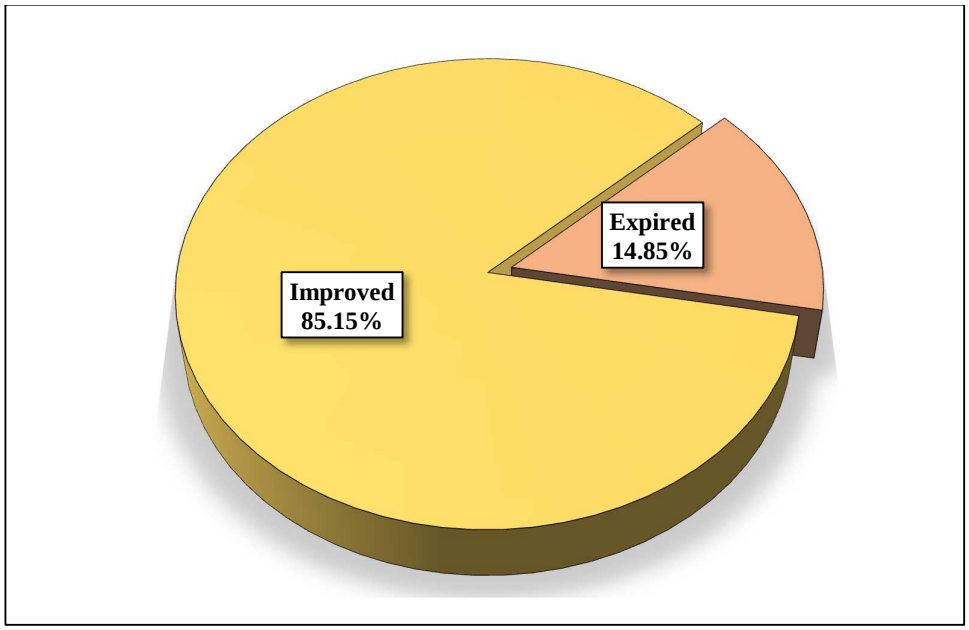

Figure 9: Distribution of subjects according to outcome.

The following table gives the distribution of demographic variables over outcome.

Table 2: Distribution of demographic variables over outcome.

Variables	**Sub Category**	**Outcome**		**Total**	**p-value**
		Expired	**Improved**		
Age (years)	Mean ± SD	59.67 ± 16.19	50.99 ± 13.95	52.28 ± 14.55	**0.0324^{t*}**
	Median (Min, Max)	60 (35, 88)	52 (19, 78)	54 (19, 88)	
Gender	Female	6 (40%)	26 (30.23%)	32 (31.68%)	0.5862^{MC}
	Male	9 (60%)	60 (69.77%)	69 (68.32%)	

*Abbreviation: t – Two sample t test, MC – Chi square test with Monte Carlo simulation, * indicates statistical significance.*

From two sample t test, it is observed that, there is significant difference in the mean age over outcome. Further, it can be noted that the mean age of expired subjects is more than those who improved.

From Chi square test, it is observed that, there is no significant difference in the distribution of gender over groups.

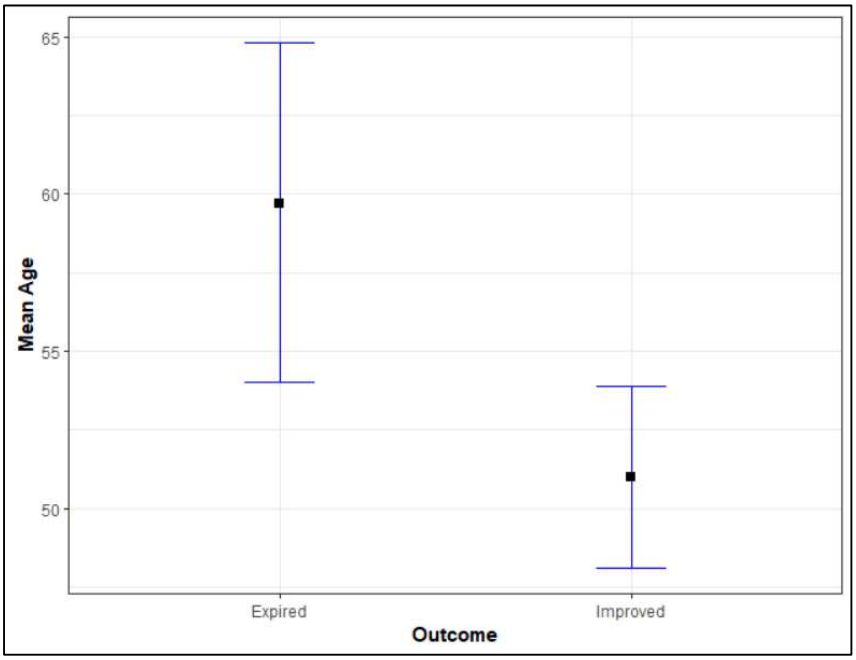

Figure 10: Mean plot of age over outcome.

In mean plot of age over outcome, the bars do not overlap on each other indicating that there is significant difference in distribution of age over outcome.

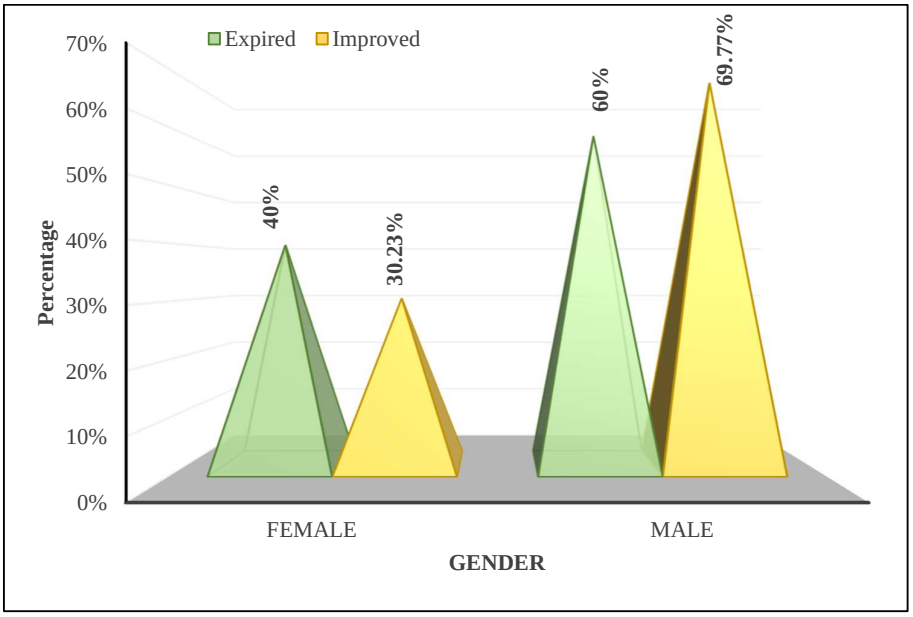

Figure 11: Distribution of gender over outcome.

Out of 15 subjects who didn't survive, 9 (60%) were males and 6 (40%) were females. Out of 86 subjects whose condition got improved, 60 (69.77%) were males and 26 (30.23%) were females.

The following table gives the association of chief complaints over outcome.

Table 3: Association of chief complaints over outcome.

Chief complaints	Outcome		Total	p-value
	Expired	Improved		
Breathlessness	10 (66.67%)	31 (36.05%)	41 (40.59%)	**0.0259[C]***
Cough	4 (26.67%)	27 (31.4%)	31 (30.69%)	0.7926[MC]
Fever	6 (40%)	53 (61.63%)	59 (58.42%)	0.1168[C]
Headache	1 (6.67%)	3 (3.49%)	4 (3.96%)	1[MC]
Giddiness	0	1 (1.16%)	1 (0.99%)	1[MC]
Hemoptysis	0	1 (1.16%)	1 (0.99%)	1[MC]
Generalized Weakness	2 (13.33%)	7 (8.14%)	9 (8.91%)	0.6202[MC]
Myalgia	0	1 (1.16%)	1 (0.99%)	1[MC]

*Abbreviation: C – Chi square test, MC – Chi square test with Monte Carlo simulation, * indicates statistical significance.*

From Chi square test, it is observed that, there is significant association of breathlessness with outcome. The odds of death are 3.5484 (95% CI: 1.1121 - 11.3220) times more for subjects with breathlessness compared to those who don't have breathlessness. There is no significant association of other complaints with outcome.

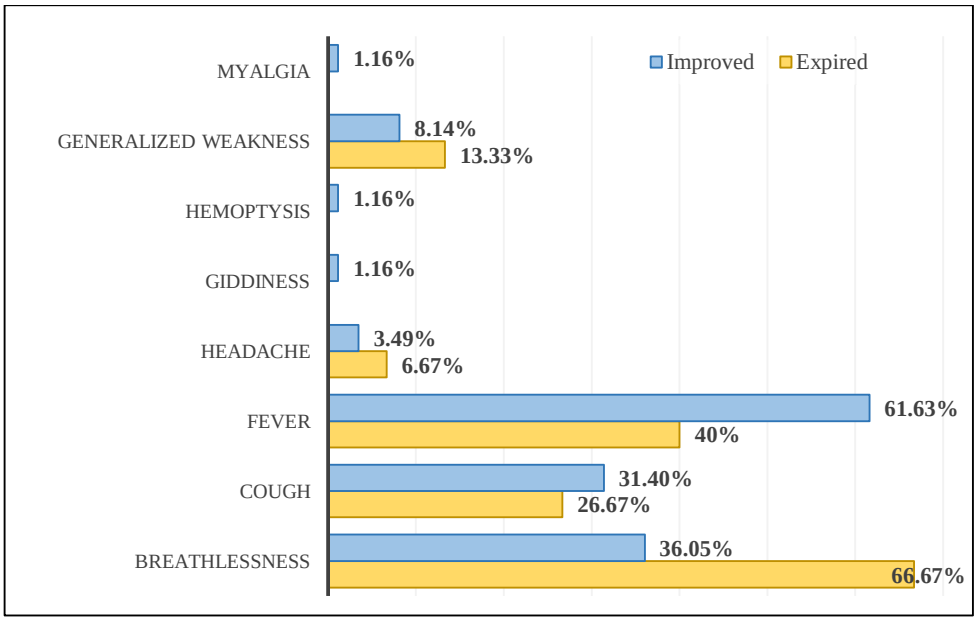

Figure 12: Distribution of chief complaints over outcome.

The following table gives the association of past history over outcome.

Table 4: Association of past history over outcome.

Past history	Outcome		Total	p-value
	Expired	Improved		
T2DM	3 (20%)	10 (11.63%)	13 (12.87%)	0.4233[MC]
Hypertension	4 (26.67%)	7 (8.14%)	11 (10.89%)	0.0665[MC]
Thyroid Disorder	0	3 (3.49%)	3 (2.97%)	1[MC]
Lymphoma	0	1 (1.16%)	1 (0.99%)	1[MC]

Abbreviation: MC – Chi square test with Monte Carlo simulation.

From Chi square test, it is observed that, there is no significant association of any past history with outcome.

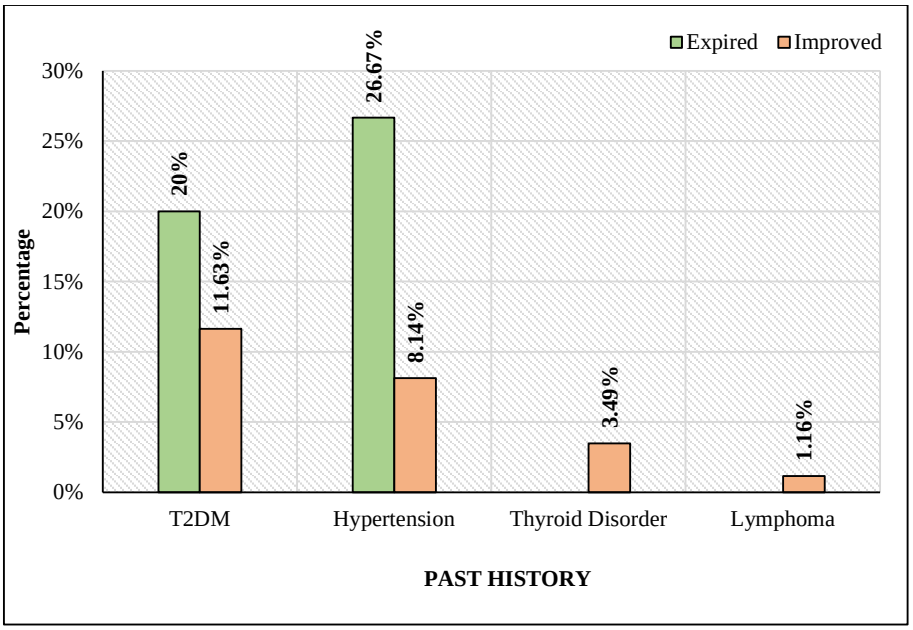

Figure 13: Distribution of past history over outcome.

The following table gives the comparison of different parameters over outcome.

Table 5: Comparison of different parameters over outcome.

Variables	Outcome		Total	p-value
	Expired	**Improved**		
Pulse rate (bpm)	99.87 ± 16.36 104 (66, 126)	89.5 ± 15.89 88 (24, 136)	91.04 ± 16.3 88 (24, 136)	**0.0212^{MW*}**
SBP	128.67 ± 20.46 130 (88, 180)	119.48 ± 17.58 120 (80, 200)	120.84 ± 18.22 120 (80, 200)	0.0713^{MW}
DBP	74.67 ± 11.25 70 (50, 90)	76.12 ± 9.45 80 (50, 106)	75.9 ± 9.69 80 (50, 106)	0.7168^{MW}
SPO2	77.6 ± 25.68 90 (24, 100)	86.34 ± 10.71 90 (54, 99)	85.04 ± 14.13 90 (24, 100)	0.7851^{MW}
Haemoglobin	11.65 ± 2.04 11.5 (8.7, 15)	12.88 ± 1.83 13.2 (8.4, 16.6)	12.69 ± 1.9 13 (8.4, 16.6)	**0.0201^{t*}**
Total Leucocyte count	11406.67 ± 4535.96 11100 (4600, 21500)	10098.84 ± 4672.61 9450 (2400, 22600)	10293.07 ± 4653.74 9700 (2400, 22600)	0.2699^{MW}
Platelet Count	218333.3 ± 63552.75 218000 (128000, 337000)	210697.7 ± 83671.07 201500 (22000, 479000)	211831.7 ± 80768.94 205000 (22000, 479000)	0.6194^{MW}
Erythrocyte Sedimentation Rate (ESR)	42.73 ± 29.26 49 (6, 87)	33.86 ± 20.22 31 (6, 91)	35.18 ± 21.85 31 (6, 91)	0.3616^{MW}
D-dimer	2751.8 ± 2929.56 1329 (522, 10524)	1110.18 ± 1471.83 551 (84, 7155)	1353.99 ± 1840.4 593 (84, 10524)	**< 0.001^{MW*}**
Interleukin - 6	256.39 ± 433.36 121.6 (1.5, 1714)	90.23 ± 145.5 36.5 (1.5, 700)	114.9 ± 218.66 45 (1.5, 1714)	**0.0065^{MW*}**
Hs- Reactive Protein	160.57 ± 73.19 176.1 (36.6, 292)	98.97 ± 74.16 86.2 (1.5, 307.1)	108.12 ± 76.88 90 (1.5, 307.1)	**0.0039^{MW*}**
Serum Ace levels	18.33 ± 8.67 19 (5, 36)	18.33 ± 12.33 16 (5, 69)	18.33 ± 11.83 16 (5, 69)	0.4526^{MW}
Total Bilirubin	0.49 ± 0.18 0.45 (0.23, 0.87)	0.56 ± 0.4 0.42 (0.11, 2.11)	0.55 ± 0.38 0.42 (0.11, 2.11)	0.6918^{MW}
Direct Bilirubin	0.26 ± 0.2 0.18 (0.1, 0.86)	0.33 ± 0.31 0.21 (0.06, 2)	0.32 ± 0.3 0.2 (0.06, 2)	0.43^{MW}
SGOT	67 ± 45 51 (17, 173)	63.7 ± 118.62 33 (0.19, 767)	64.19 ± 110.65 36 (0.19, 767)	0.9158^{MW}

SGPT	44.33 ± 32.45 42 (10, 139)	55.71 ± 108.94 29 (9, 630)	54.02 ± 101.25 30 (9, 630)	0.3616^{MW}
Alkaline Phosphatase	111.93 ± 97.14 90 (38, 453)	105.83 ± 44.19 100 (19, 280)	106.73 ± 54.64 100 (19, 453)	0.3437^{MW}
Serum Albumin	3.4 ± 0.45 3.3 (2.6, 4)	3.78 ± 0.45 3.85 (2.5, 4.62)	3.73 ± 0.47 3.8 (2.5, 4.62)	**0.0057^{MW*}**
Urea	62.17 ± 45.82 41 (11.5, 183)	41.05 ± 24.82 35.5 (10, 168)	44.18 ± 29.57 39 (10, 183)	0.0612^{MW}
Creatinine	1.94 ± 2.65 0.98 (0.47, 10.89)	1 ± 0.88 0.81 (0.15, 6.6)	1.14 ± 1.32 0.82 (0.15, 10.89)	0.0772^{MW}

*Abbreviation: MW – Mann Whitney U test, t – Two sample t test, * indicates statistical significance.*

From Mann Whitney U test, it is observed that, there is significant difference in the distribution of pulse rate, D-dimer, Interleukin-6, Hs-Reactive protein and serum albumin over outcome. There is no significant difference in the distribution of systolic blood pressure, diastolic blood pressure, SPO2, TLC, Platelet count, ESR, serum ace level, total bilirubin, direct bilirubin, SGOT, SGPT, alkaline phosphatase, urea and creatinine over outcome.

From two sample t test, it is observed that, there is significant difference in mean HB over outcome.

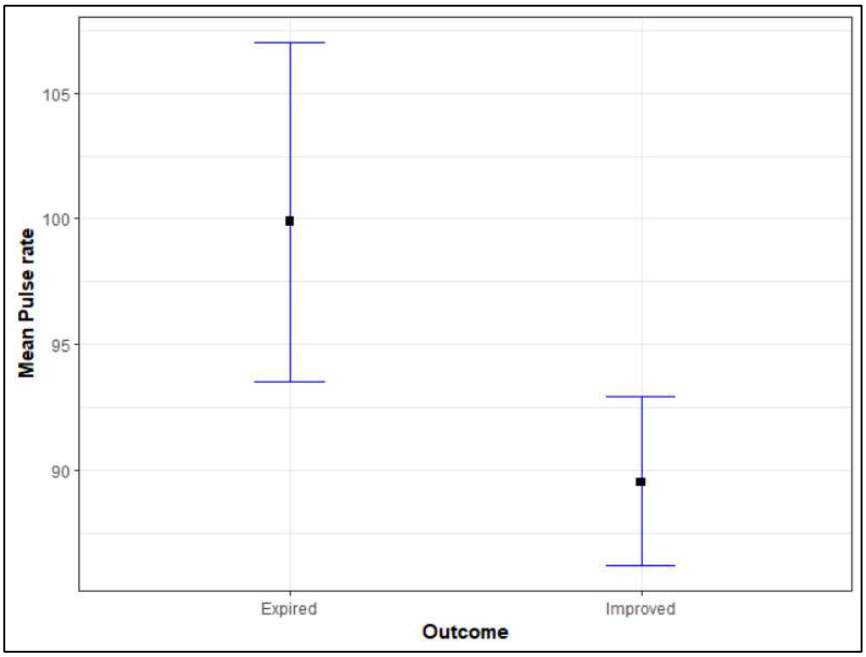

Figure 14: Mean plot of pulse rate over outcome.

In mean plot of pulse rate over outcome, the bars do not overlap on each other indicating that there is significant difference in distribution of pulse rate over outcome.

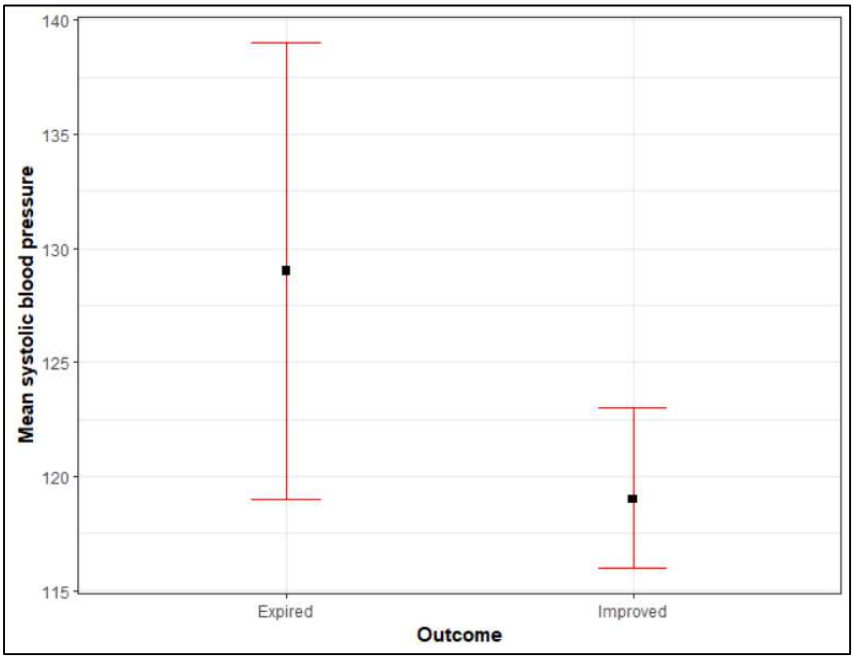

Figure 15: Mean plot of SBP over outcome.

In mean plot of SBP over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of SBP over outcome.

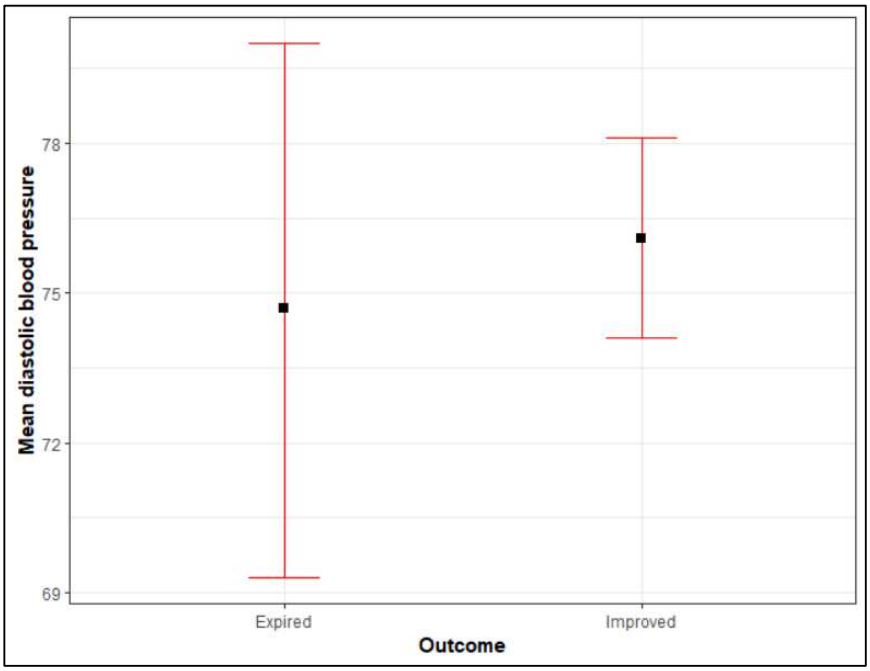

Figure 16: Mean plot of DBP over outcome.

In mean plot of DBP over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of DBP over outcome.

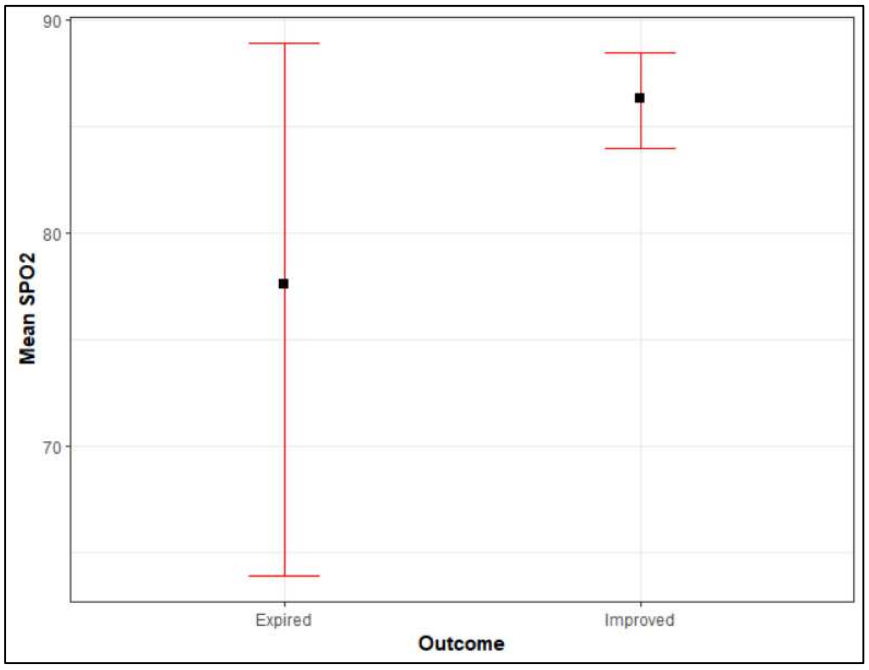

Figure 17: Mean plot of SPO2 over outcome.

In mean plot of SPO2 over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of SPO2 over outcome.

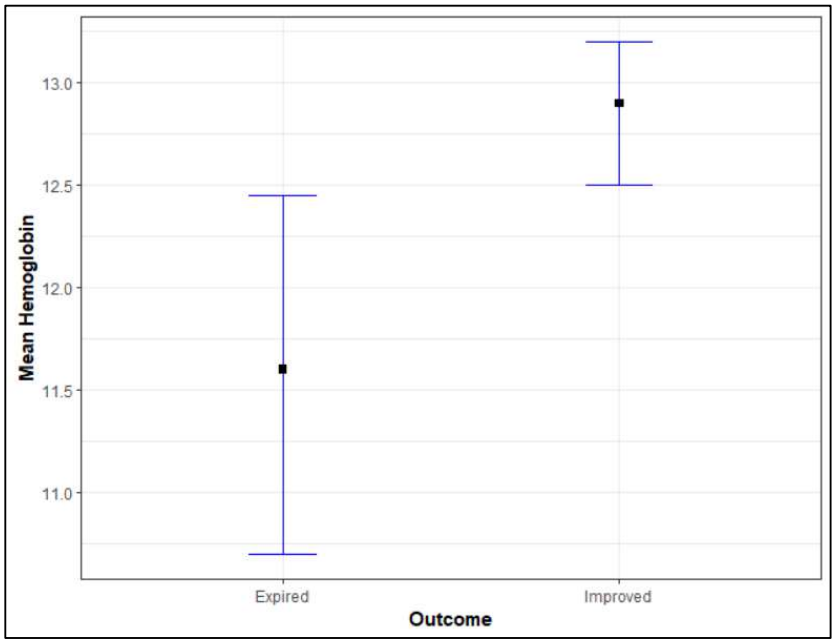

Figure 18: Mean plot of Haemoglobin over outcome.

In mean plot of Haemoglobin over outcome, the bars do not overlap on each other indicating that there is significant difference in distribution of Haemoglobin over outcome.

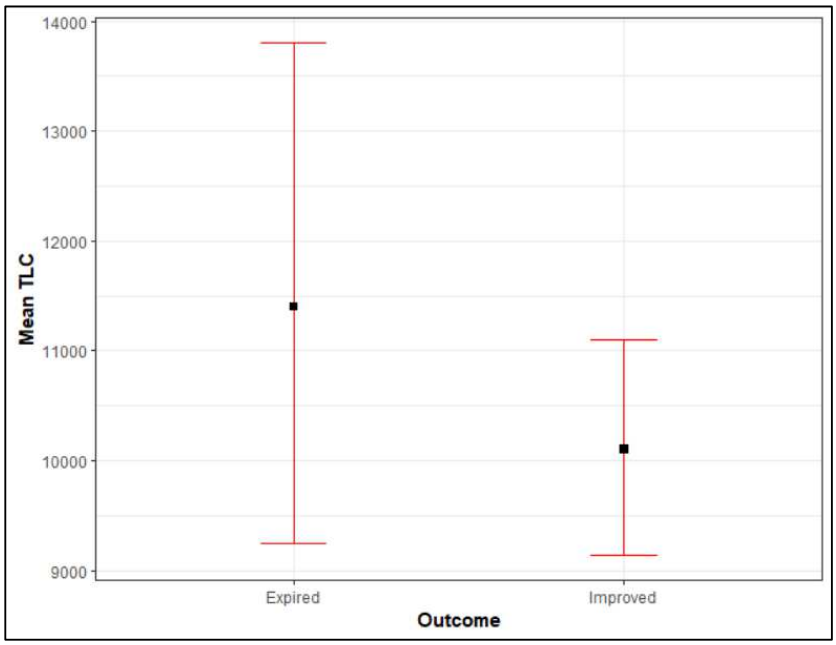

Figure 19: Mean plot of Total Leucocyte count over outcome.

In mean plot of Total Leucocyte count over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of TLC over outcome.

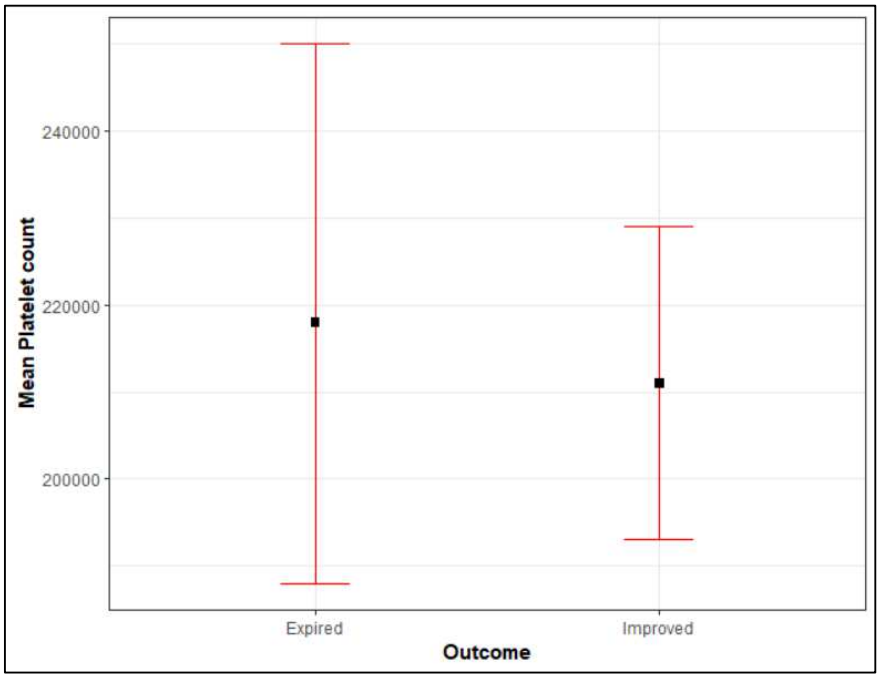

Figure 20: Mean plot of Platelet Count over outcome.

In mean plot of Platelet Count over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of Haemoglobin over outcome.

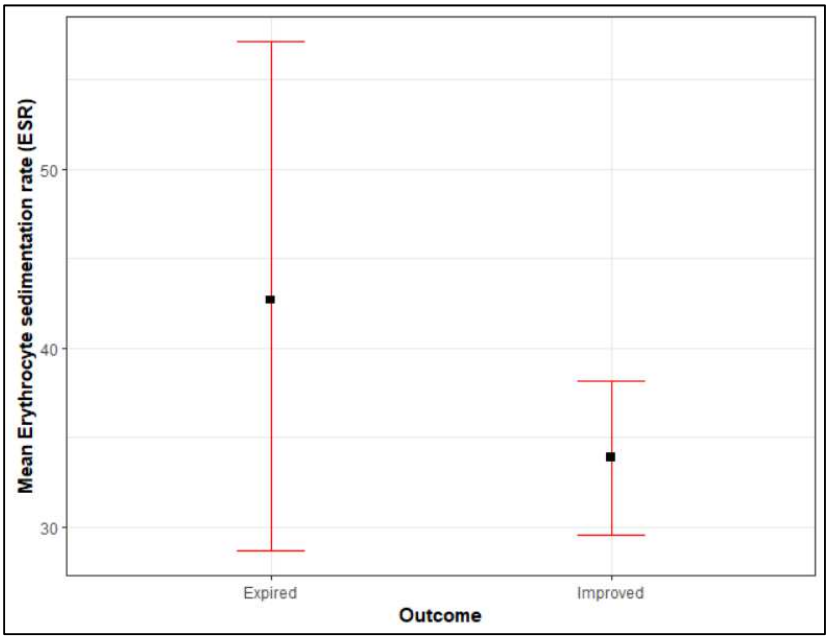

Figure 21: Mean plot of Erythrocyte Sedimentation Rate (ESR) over outcome.

In mean plot of Erythrocyte Sedimentation Rate (ESR) over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of Erythrocyte Sedimentation Rate (ESR) over outcome.

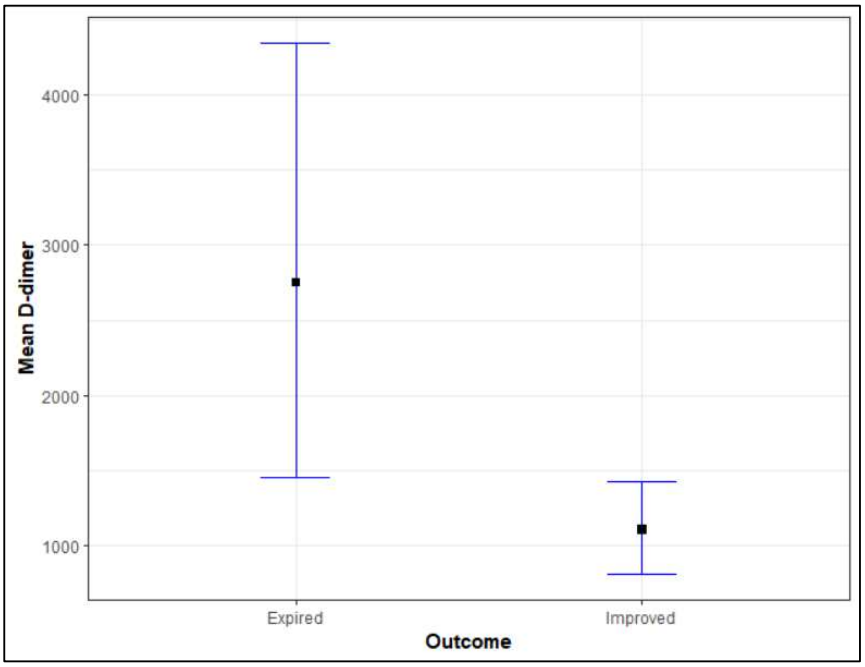

Figure 22: Mean plot of D-dimer over outcome.

In mean plot of D-dimer over outcome, the bars do not overlap on each other indicating that there is significant difference in distribution of D-dimer over outcome.

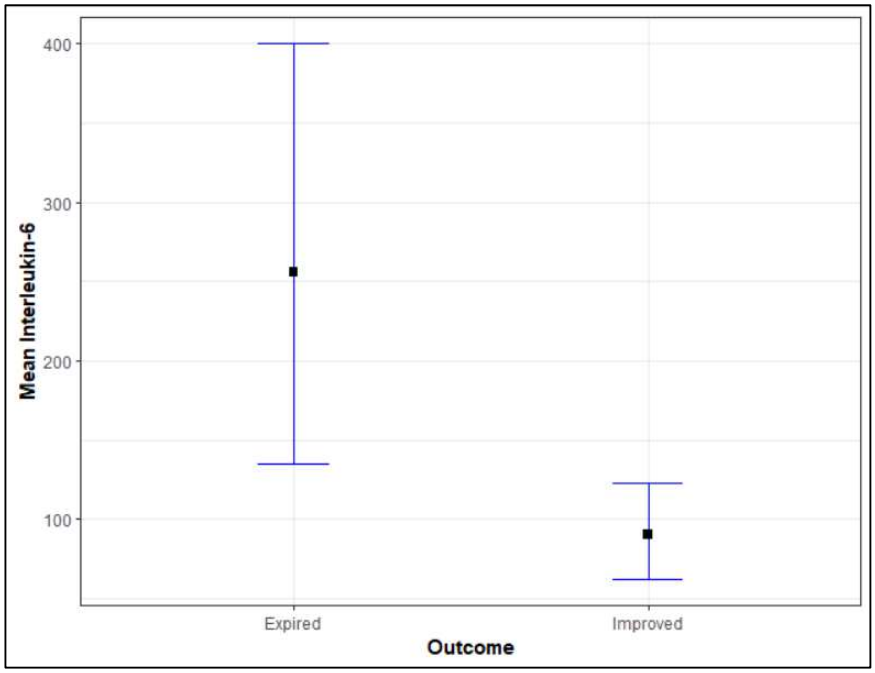

Figure 23: Mean plot of Interleukin – 6 over outcome.

In mean plot of Interleukin – 6 over outcome, the bars do not overlap on each other indicating that there is significant difference in distribution of Interleukin – 6 over outcome.

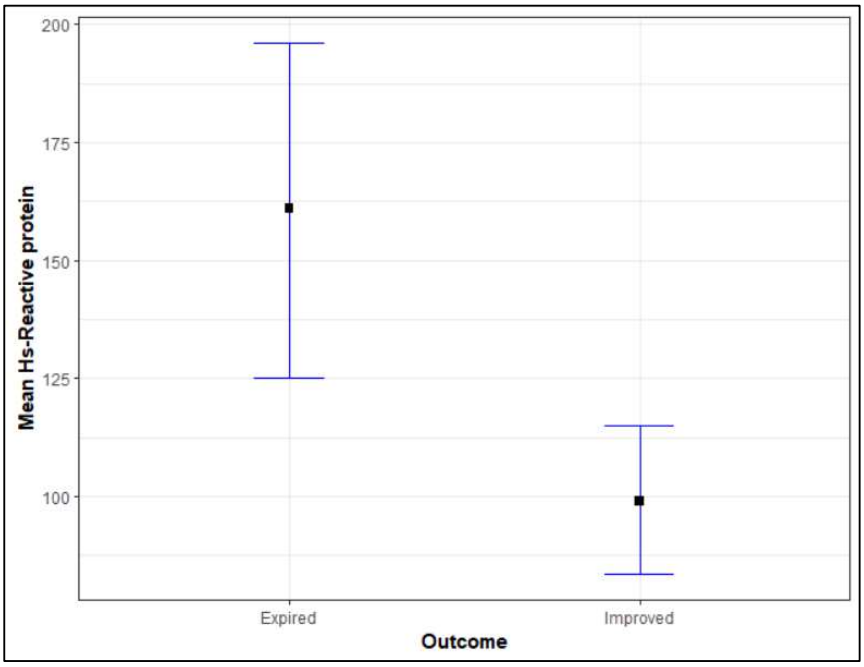

Figure 24: Mean plot of Hs- Reactive Protein over outcome.

In mean plot of Hs- Reactive Protein over outcome, the bars do not overlap on each other indicating that there is significant difference in distribution of Hs- Reactive Protein over outcome.

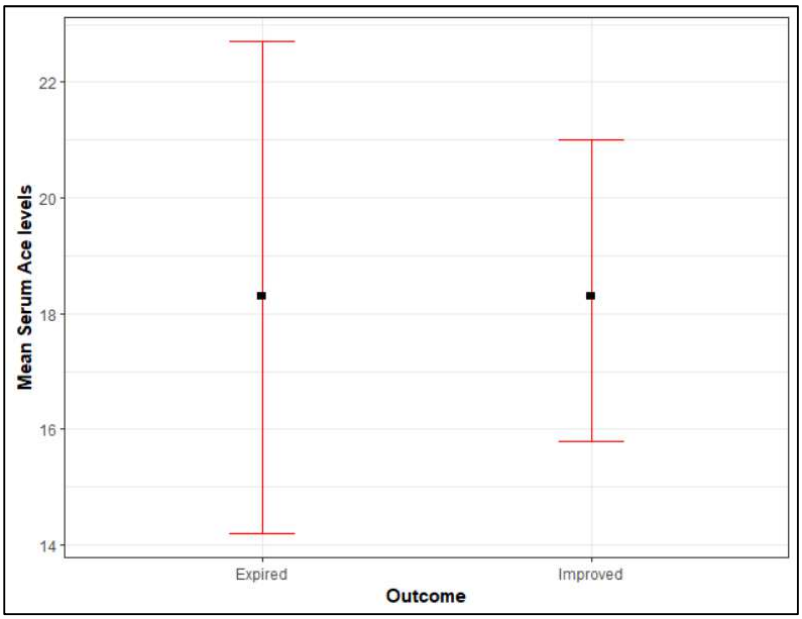

Figure 25: Mean plot of Serum Ace levels over outcome.

In mean plot of Serum Ace levels over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of Serum Ace levels over outcome.

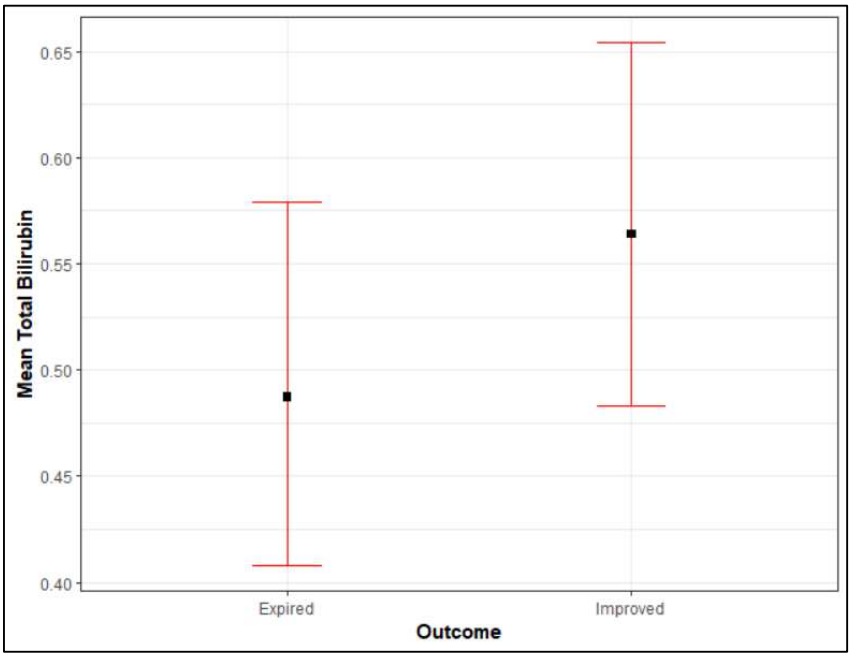

Figure 26: Mean plot of Total Bilirubin over outcome.

In mean plot of Total Bilirubin over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of Total Bilirubin over outcome.

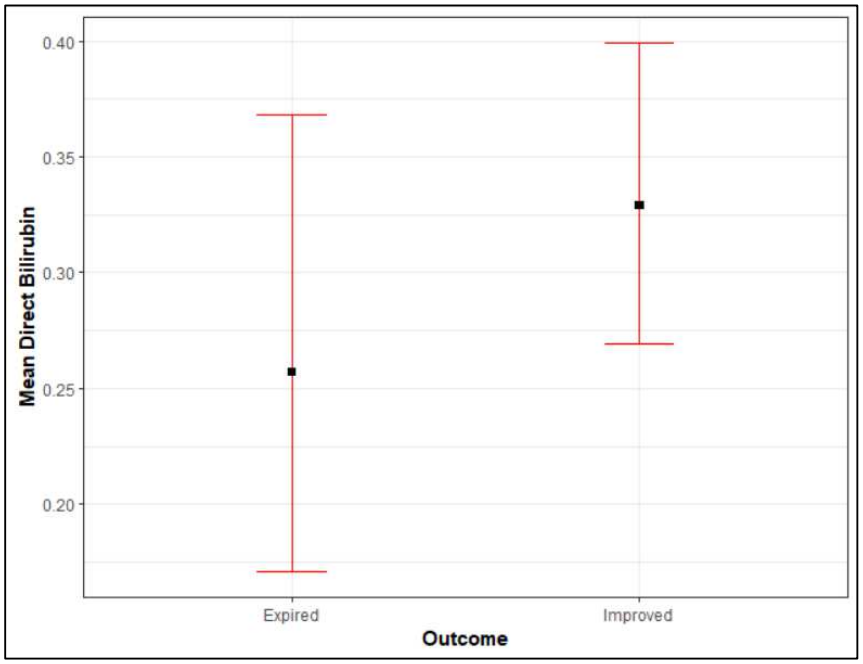

Figure 27: Mean plot of Direct Bilirubin over outcome.

In mean plot of Direct Bilirubin over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of Direct Bilirubin over outcome.

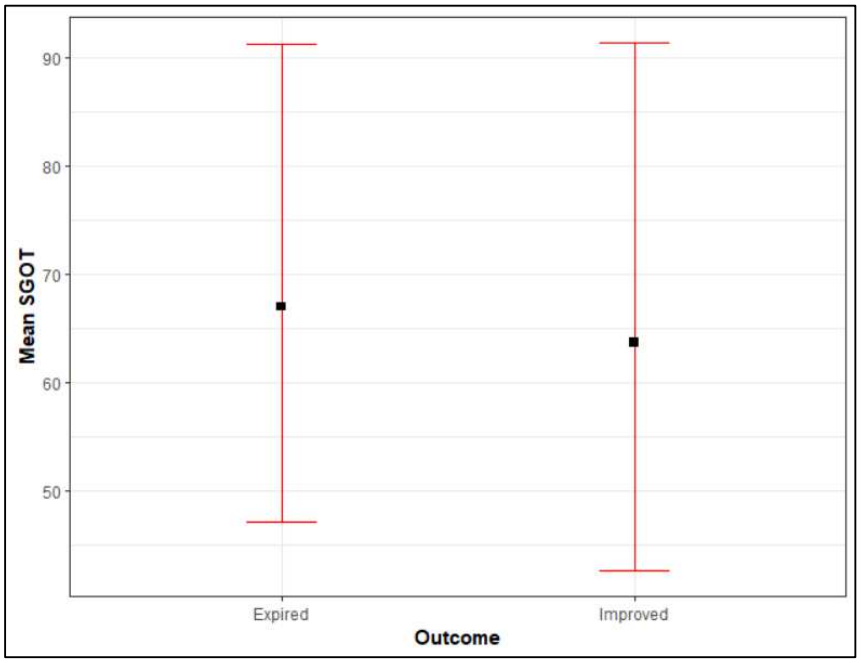

Figure 28: Mean plot of SGOT over outcome.

In mean plot of SGOT over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of SGOT over outcome.

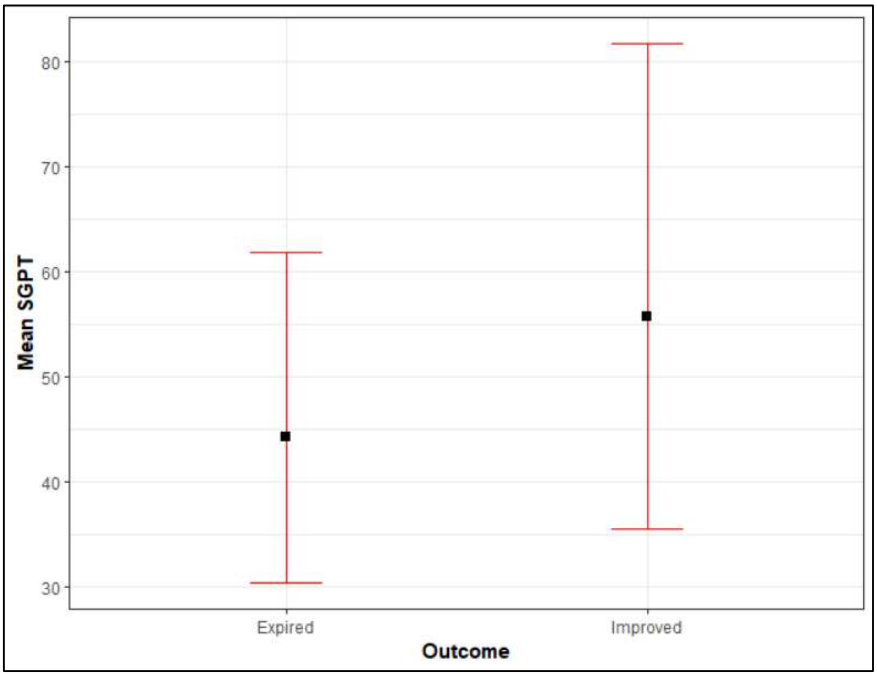

Figure 29: Mean plot of SGPT over outcome.

In mean plot of SGPT over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of SGPT over outcome.

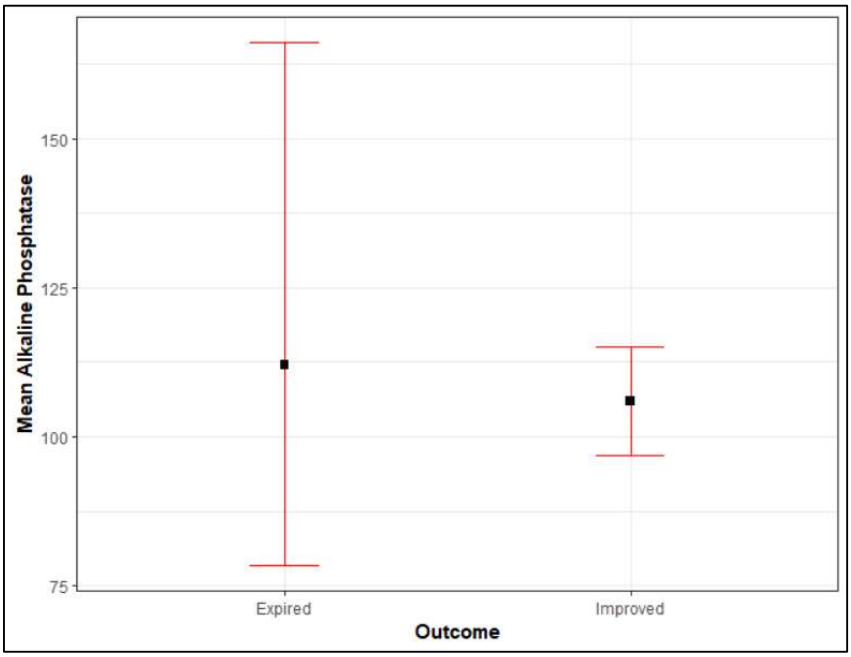

Figure 30: Mean plot of Alkaline Phosphatase over outcome.

In mean plot of Alkaline Phosphatase over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of Alkaline Phosphatase over outcome.

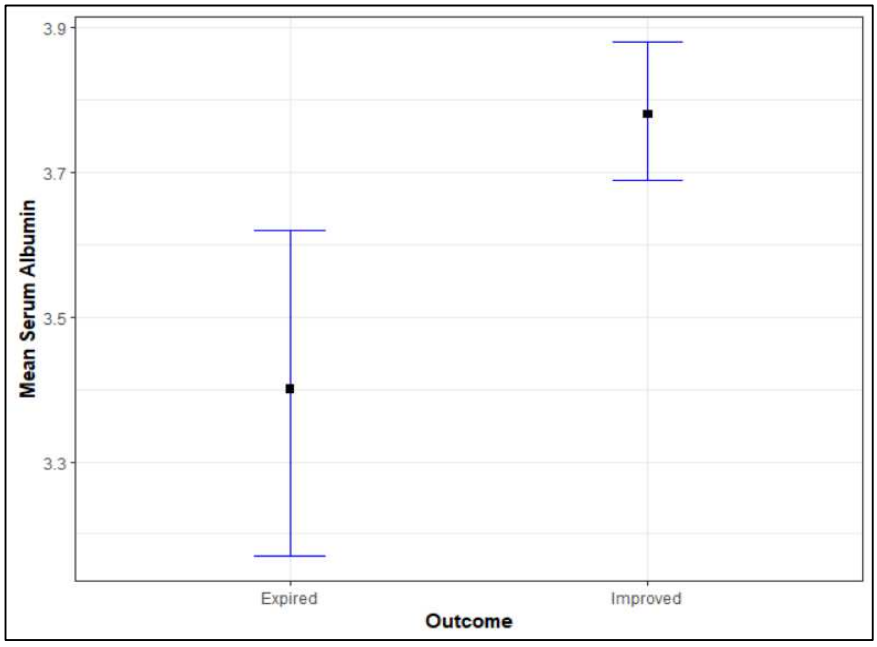

Figure 31: Mean plot of Serum Albumin over outcome.

In mean plot of Serum Albumin over outcome, the bars do not overlap on each other indicating that there is significant difference in distribution of Serum Albumin over outcome.

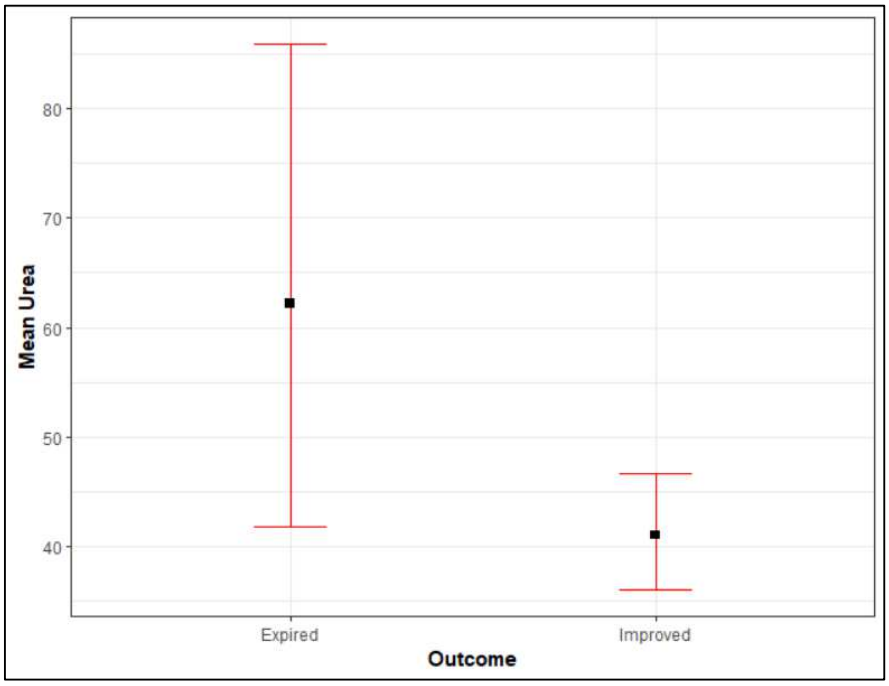

Figure 32: Mean plot of Urea over outcome.

In mean plot of Urea over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of Urea over outcome.

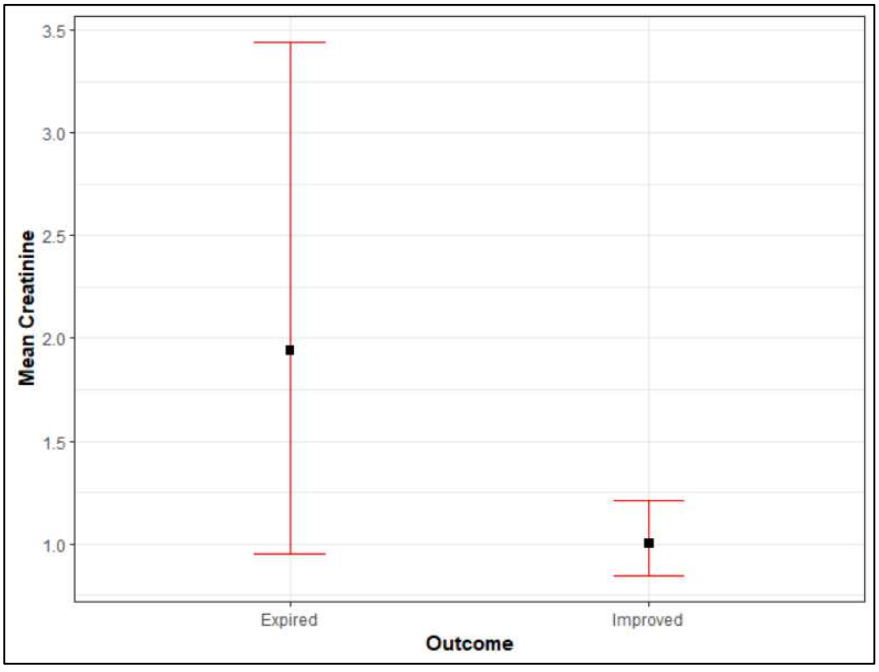

Figure 33: Mean plot of Creatinine over outcome.

In mean plot of Creatinine over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of Creatinine over outcome.

The following table gives the comparison of CT severity score over outcome.

Table 6: Comparison of CT severity score over outcome.

CT Severity score	Outcome		Total	p-value
	Expired	Improved		
Mild	2 (13.33%)	15 (17.44%)	17 (16.83%)	0.7046[MC]
Moderate	9 (60%)	41 (47.67%)	50 (49.5%)	
Severe	4 (26.67%)	30 (34.88%)	34 (33.66%)	
Mean ± SD	13.4 ± 5.34	13.23 ± 5.16	13.26 ± 5.16	0.9084[t]
Median (Min, Max)	13 (4, 24)	13 (4, 24)	13 (4, 24)	

Abbreviation: MC – Chi square test with Monte Carlo simulation, t – Two sample t test.

From Chi square test, it is observed that, there is no significant difference in the distribution of CT severity score over outcome.

From two sample t test, it is observed that, there is no significant difference in mean CT severity score over outcome.

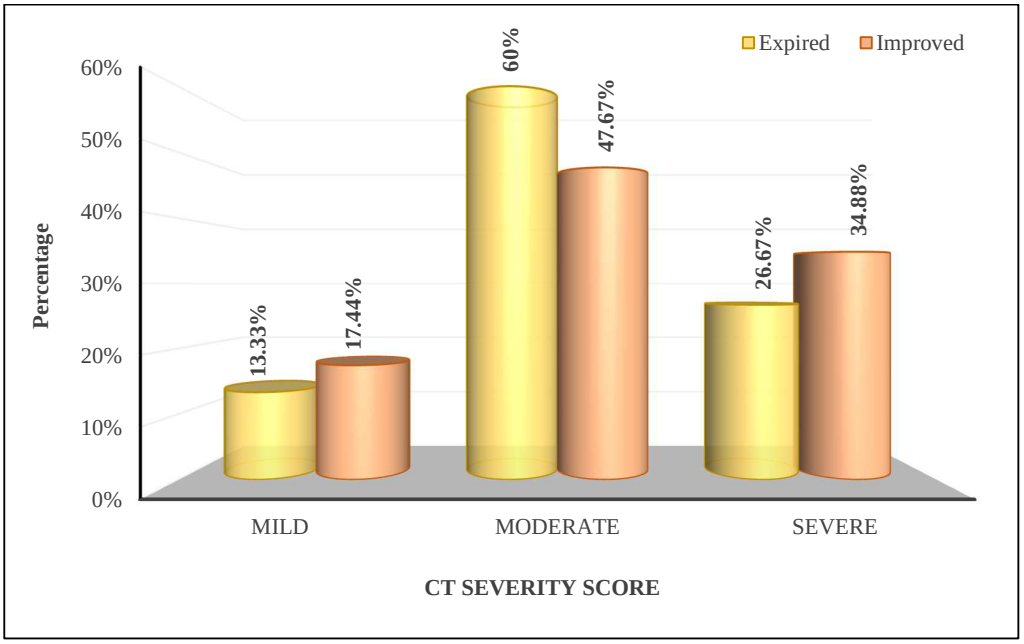

Figure 34: Distribution of CT severity score over outcome.

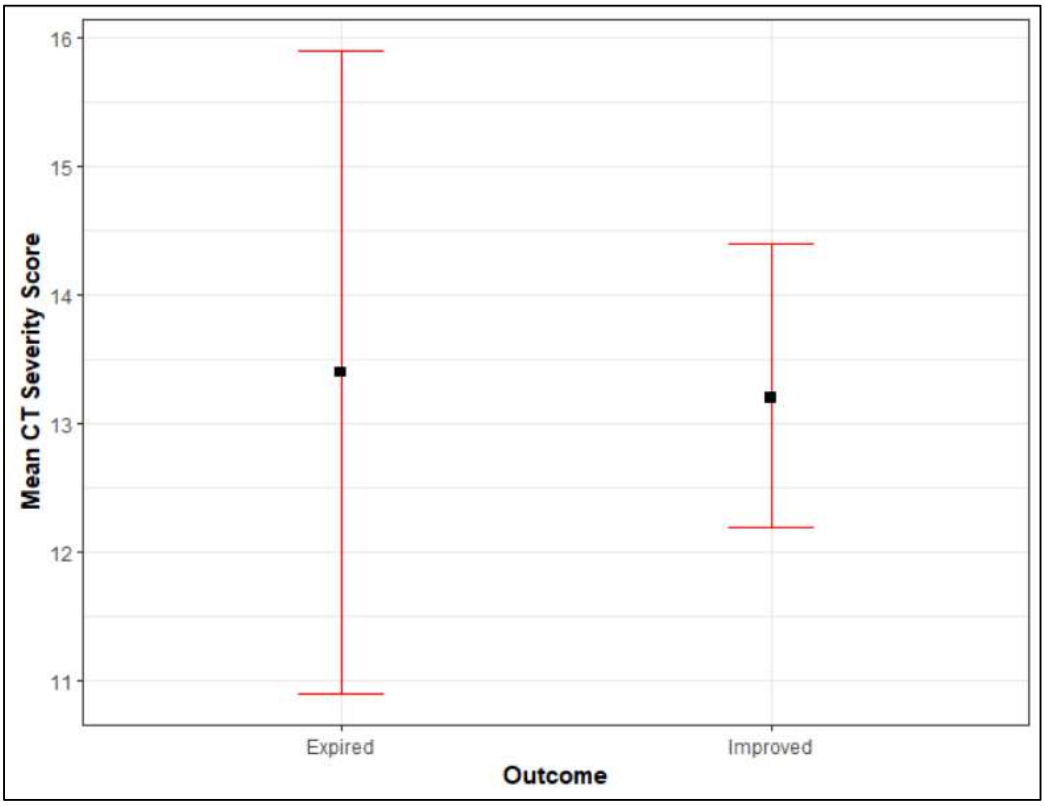

Figure 35: Mean plot of CT severity score over outcome.

In mean plot of CT severity score over outcome, the bars overlap on each other indicating that there is no significant difference in distribution of CT severity score over outcome.

The following table gives the result of logistic regression for predicting outcome.

Table 7: Result of logistic regression for predicting outcome.

Variable	Odds Ratio (95% CI)	p-value
Serum Ace Levels	1.0001 (0.9474 - 1.0433)	0.9981

From logistic regression, it is observed that, serum ace level has no significant effect on mortality (p-value = 0.9981).

Note: The AUC for serum ace level is found to be 0.5609 (95% CI: 0.3923-0.7294) in predicting mortality outcome. Hence, it is not a good predictor for mortality outcome.

The following table gives the comparison of serum ace level over CT severity score.

Table 8: Comparison of serum ace level over CT severity score.

CT Severity score	Serum Ace levels		p-value
	Mean ± SD	Median (Min, Max)	
Mild	15.47 ± 5.62	16 (5, 24)	0.9436^{K}
Moderate	18.6 ± 12.98	16 (5, 69)	
Severe	19.35 ± 12.36	16 (7, 63)	

Abbreviation: K – Kruskal Wallis test.

From Kruskal Wallis test, it is observed that, there is no significant difference in the distribution of serum ace levels over CT severity score.

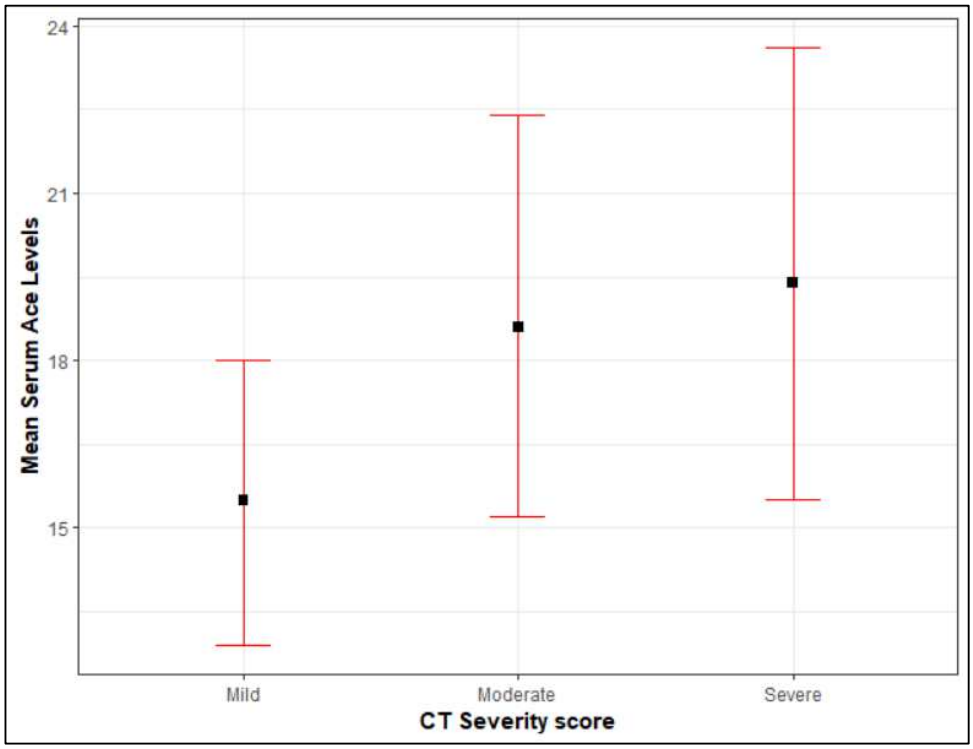

Figure 36: Mean plot of serum ace levels over CT severity score.

In mean plot of serum ace levels over CT severity score, the bars overlap on each other indicating that there is no significant difference in distribution of serum ace levels over CT severity score.

The following table gives the correlation of different parameters with serum ace levels.

Table 9: Correlation of different parameters with serum ace levels.

Variables	Correlation coefficient	p-value ^{SP}
Pulse rate (bpm)	0.1207	0.2293
SBP	0.0813	0.4192
DBP	0.1337	0.1826
SPO2	0.0090	0.9292
Haemoglobin	-0.2366	**0.0172***
Total Leucocyte count	-0.0883	0.3801
Platelet Count	0.0011	0.9915
Erythrocyte Sedimentation Rate (ESR)	0.0686	0.4952
D-dimer	-0.0848	0.399
Interleukin - 6	0.0175	0.8624
Hs- Reactive Protein	-0.0940	0.3498
CT severity score	0.0463	0.6457
Total Bilirubin	-0.1466	0.1435
Direct Bilirubin	-0.0828	0.4104
SGOT	-0.0865	0.3896
SGPT	-0.1783	0.0745
Alkaline Phosphatase	0.2791	**0.0047***
Serum Albumin	0.1163	0.2468
Urea	0.1237	0.2178
Creatinine	0.0374	0.7107

*Abbreviation: SP – Spearman's rank correlation test, * indicates statistical significance.*

From Spearman's rank correlation test, it is observed that, there is significant low negative correlation between haemoglobin and serum ace levels. There is significant low positive correlation between alkaline phosphatase and serum ace levels. However, there is no significant correlation between serum ace levels and other parameters.

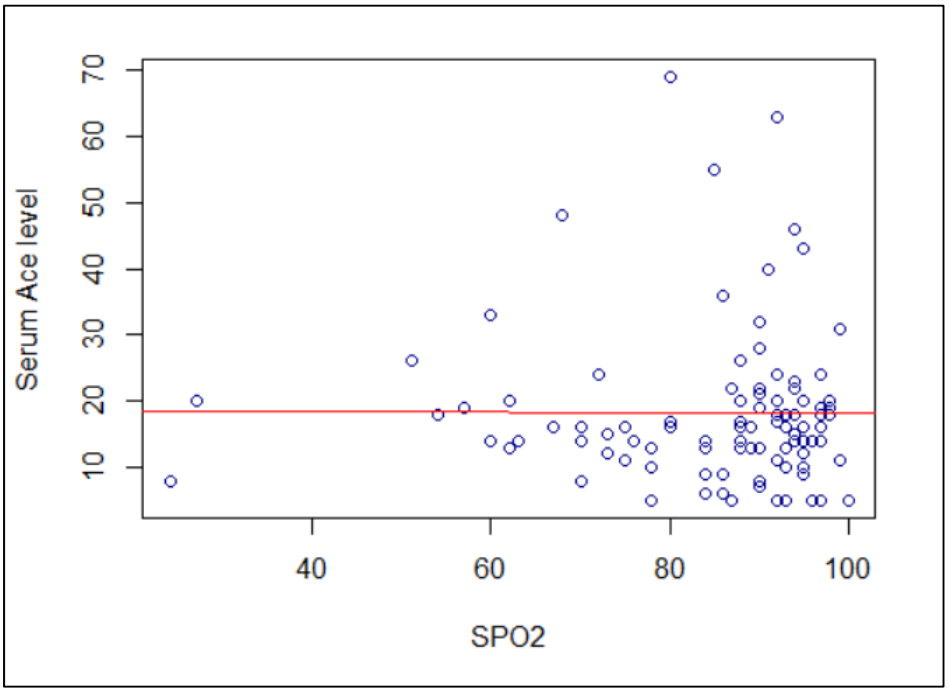

Figure 37: Scatter plot of SPO2 with serum ace levels.

The regression line is a line almost parallel to x axis indicating that there is no significant correlation between SPO2 and serum ace levels.

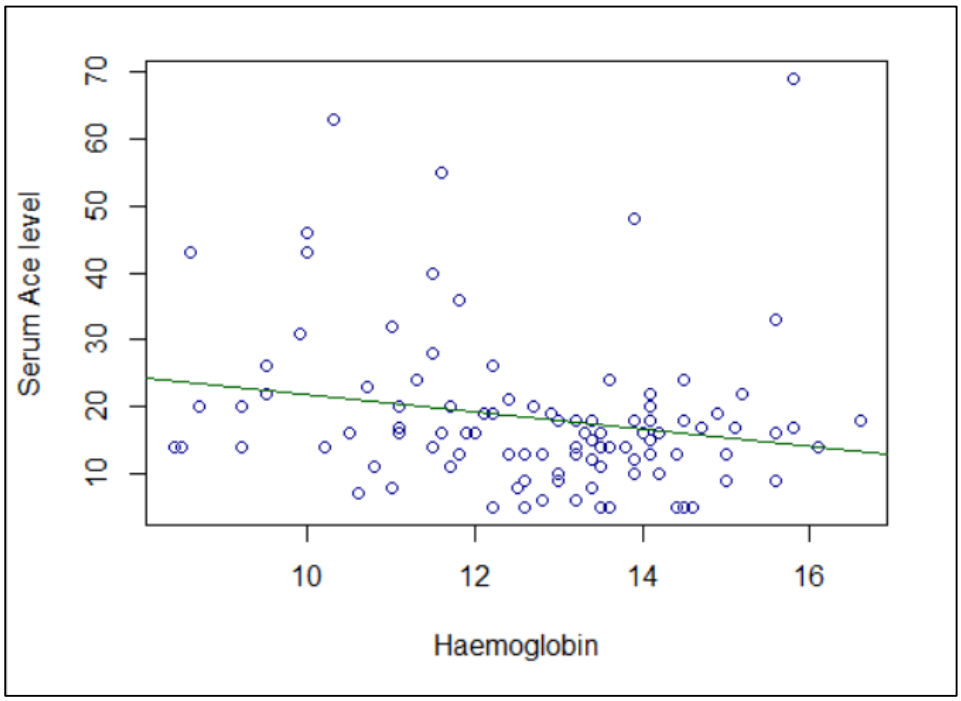

Figure 38: Scatter plot of Haemoglobin with serum ace levels.

The regression line has downward slope indicating that there is negative correlation between haemoglobin and serum ace levels.

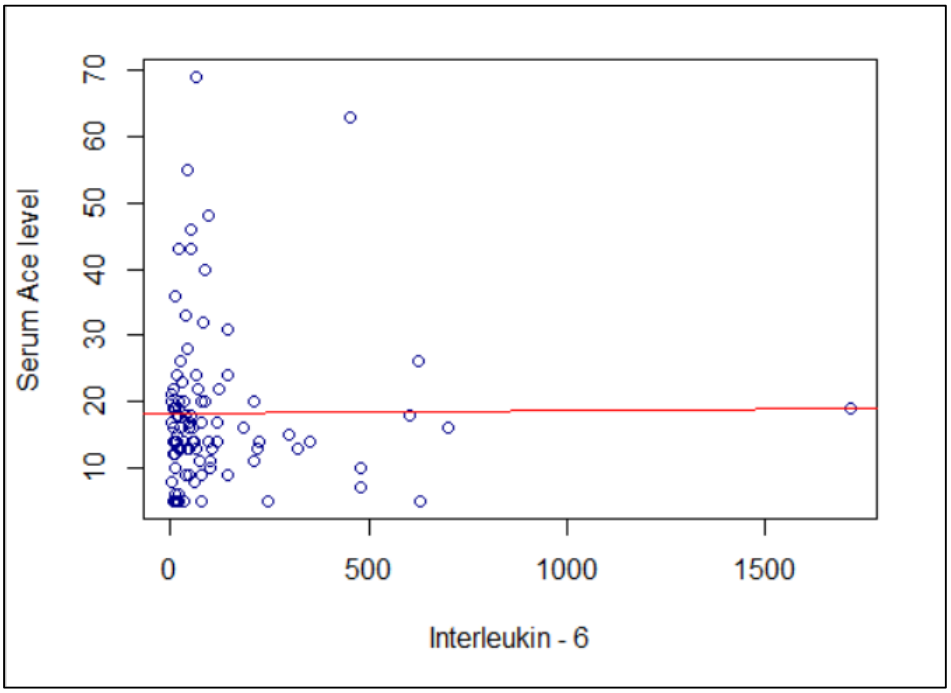

Figure 39: Scatter plot of Interleukin-6 with serum ace levels.

The regression line is a line almost parallel to x axis indicating that there is no significant correlation between IL-6 and serum ace levels.

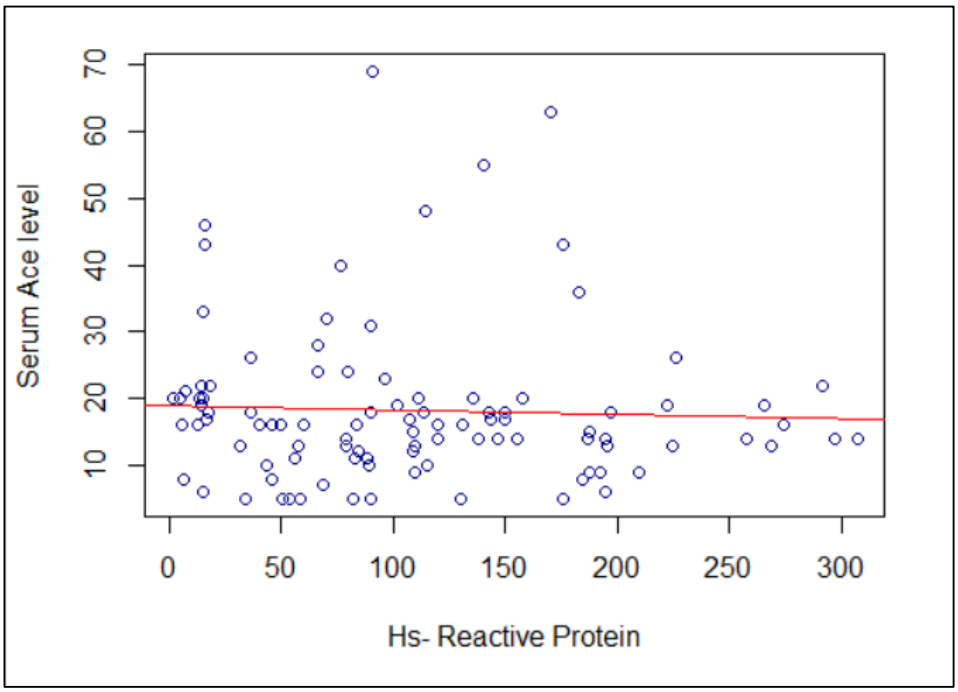

Figure 40: Scatter plot of Hs-Reactive protein with serum ace levels.

The regression line is a line almost parallel to x axis indicating that there is no significant correlation between Hs-Reactive protein and serum ace levels.

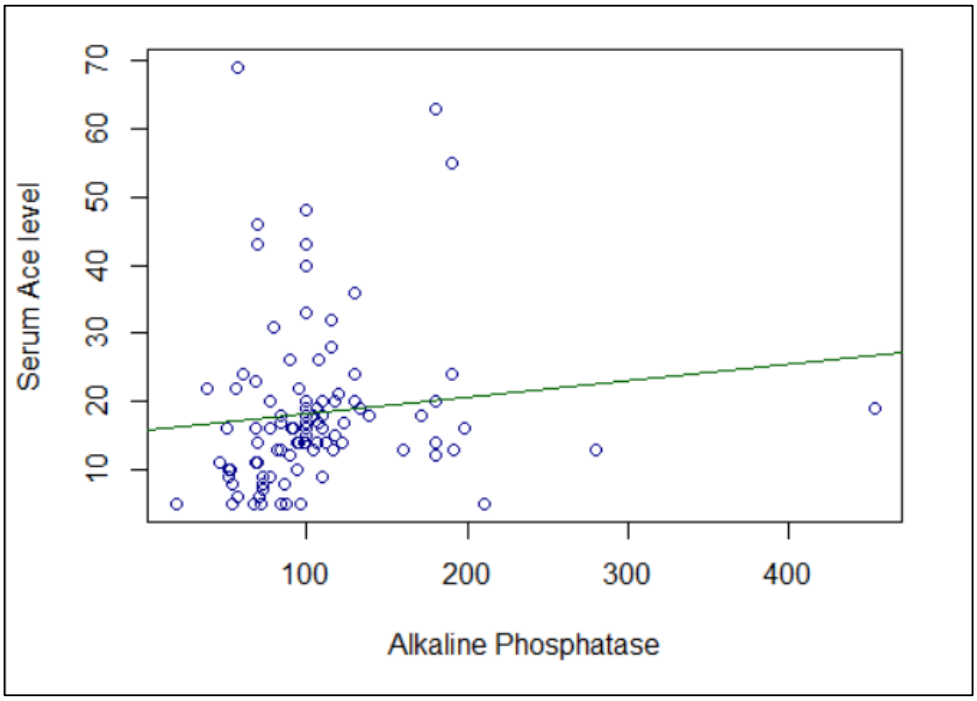

Figure 41: Scatter plot of alkaline phosphatase with serum ace levels.

The regression line has upward slope indicating that there is positive correlation between alkaline phosphatase and serum ace levels.

The following table gives the comparison of different parameters over CT severity score.

Table 10: Comparison of different parameters over CT severity score.

Variables	CT severity score			p-value
	Mild	Moderate	Severe	
Pulse rate (bpm)	87.65 ± 7.01 88 (78, 100)	95.5 ± 17.13 90 (66, 136)	86.18 ± 16.91 88 (24, 126)	**0.0484[K]***
SBP	120 ± 18.37 120 (90, 160)	122.14 ± 16.02 120 (80, 180)	119.35 ± 21.37 111 (88, 200)	0.2128[K]
DBP	76.47 ± 10.57 80 (60, 90)	76.76 ± 9.91 80 (50, 106)	74.35 ± 8.98 70 (50, 100)	0.3193[K]
SPO2	85.06 ± 12.34 92 (60, 95)	87.54 ± 13.12 92 (27, 100)	81.35 ± 15.86 87.5 (24, 99)	0.0700[K]
Haemoglobin	13.06 ± 2.1 13.4 (8.5, 16.1)	12.6 ± 1.74 12.75 (8.7, 15.8)	12.65 ± 2.07 13.1 (8.4, 16.6)	0.6028[K]
Total Leucocyte count	10405.88 ± 5914.23 7700 (3500, 22600)	10004 ± 4358.34 9050 (3100, 21500)	10661.76 ± 4493.43 11500 (2400, 21600)	0.7146[K]
Platelet Count	204529.41 ± 83635.46 200000 (117000, 452000)	218800 ± 72848.18 214000 (33000, 479000)	205235.29 ± 91385.65 196000 (22000, 426000)	0.4438[K]
ESR	30.71 ± 16.16 25 (6, 66)	36.42 ± 23.09 32.5 (6, 91)	35.59 ± 22.72 33.5 (7, 87)	0.8232[K]
D-dimer	1140.71 ± 1530.99 518 (159, 5000)	1122.9 ± 1443.03 553 (84, 5000)	1800.46 ± 2392.84 815.5 (235, 10524)	0.0742[K]
Interleukin - 6	81.87 ± 66.88 68 (10, 223.8)	107.21 ± 263.49 41 (1.5, 1714)	142.73 ± 195.39 42.75 (1.5, 700)	0.3411[K]
Hs- Reactive Protein	108.7 ± 84.2 111.5 (13, 292)	97.64 ± 74.94 82.75 (1.5, 297)	123.24 ± 75.69 109 (5.7, 307.1)	0.2651[K]
Total Bilirubin	0.78 ± 0.56 0.5 (0.19, 2.11)	0.48 ± 0.27 0.4 (0.11, 1.33)	0.55 ± 0.38 0.41 (0.15, 1.9)	0.1027[K]
Direct Bilirubin	0.43 ± 0.46 0.27 (0.06, 2)	0.28 ± 0.22 0.2 (0.06, 1.1)	0.32 ± 0.29 0.21 (0.06, 1.2)	0.2562[K]
SGOT	61.94 ± 81.86 31 (12, 339)	61.84 ± 108.58 33 (0.19, 759)	68.76 ± 127.73 41 (10, 767)	0.6657[K]
SGPT	66.29 ± 136.35 26 (9, 587)	50.88 ± 87.2 27.5 (10, 600)	52.5 ± 103.28 32.5 (13, 630)	0.6994[K]
Alkaline Phosphatase	99.18 ± 62.4 95 (38, 280)	107.92 ± 62.51 98 (19, 453)	108.76 ± 36.35 100 (52, 198)	0.2984[K]
Serum Albumin	3.62 ± 0.49 3.7 (2.5, 4.3)	3.74 ± 0.47 3.8 (2.8, 4.62)	3.76 ± 0.45 3.9 (2.5, 4.5)	0.7214[K]

Urea	39.41 ± 25.61 31 (14, 102)	44.3 ± 30.13 38.5 (10, 183)	46.4 ± 31.09 41 (11.5, 168)	0.5702[K]
Creatinine	0.99 ± 0.72 0.81 (0.46, 3.72)	1.25 ± 1.68 0.84 (0.15, 10.89)	1.07 ± 0.91 0.82 (0.47, 5.4)	0.9387[K]

*Abbreviation: K – Kruskal Wallis test, * indicates statistical significance.*

From Kruskal Wallis test, there is significant difference in the distribution of pulse rate over CT severity score. Further. From Dunn test, it is observed that, there is significant difference in pulse rate between mild and moderate severity (p-value = 0.0304).

There is no significant difference in the distribution of other parameters over CT severity score.

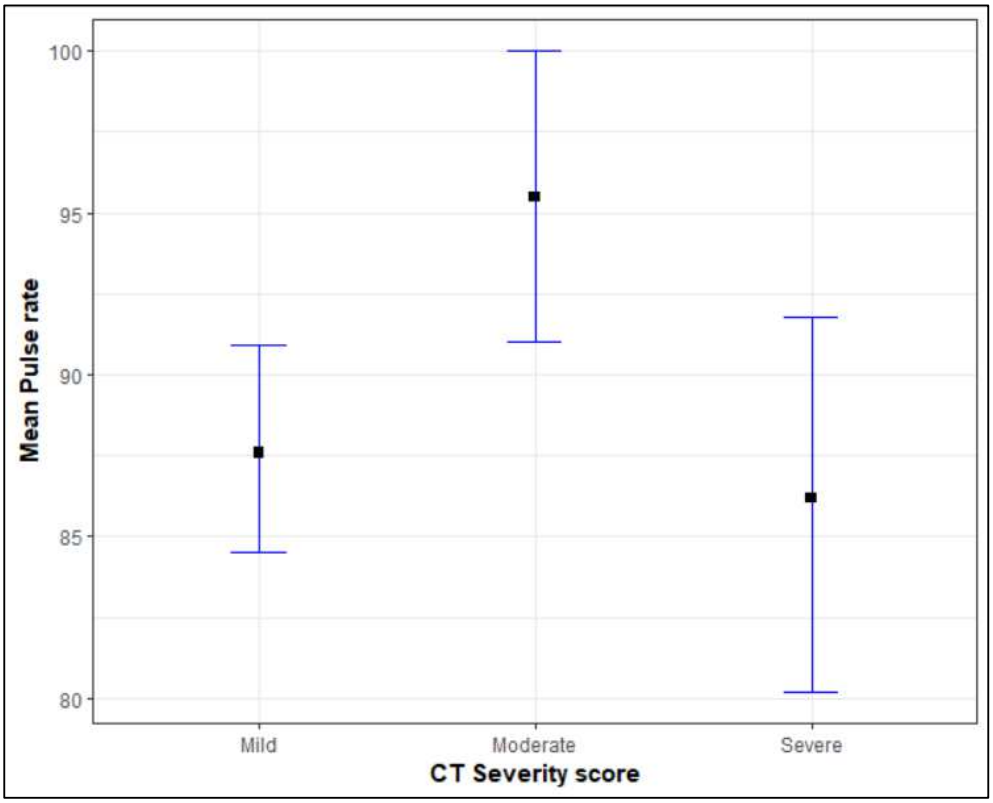

Figure 42: Mean plot of pulse rate over CT severity score.

In mean plot of pulse rate over CT severity score, the bars of mild and moderate do not overlap on each other indicating that there is significant difference in distribution of pulse rate of subjects with mild and moderate severity.

The following table gives the comparison of serum ace levels over Age.

Table 11: Comparison of serum ace levels over Age.

Age (years)	Serum Ace levels		p-value
	Mean ± SD	Median (Min, Max)	
≤ 30	24.43 ± 13.49	20 (6, 48)	0.1611[K]
30-49	16.59 ± 11.75	14.5 (5, 69)	
50-69	19.35 ± 12.44	16 (5, 63)	
70-89	15.58 ± 7.09	14 (5, 26)	

Abbreviation: K – Kruskal Wallis test.

From Kruskal Wallis test, it is observed that, there is no significant difference in the distribution of serum ace levels over age groups.

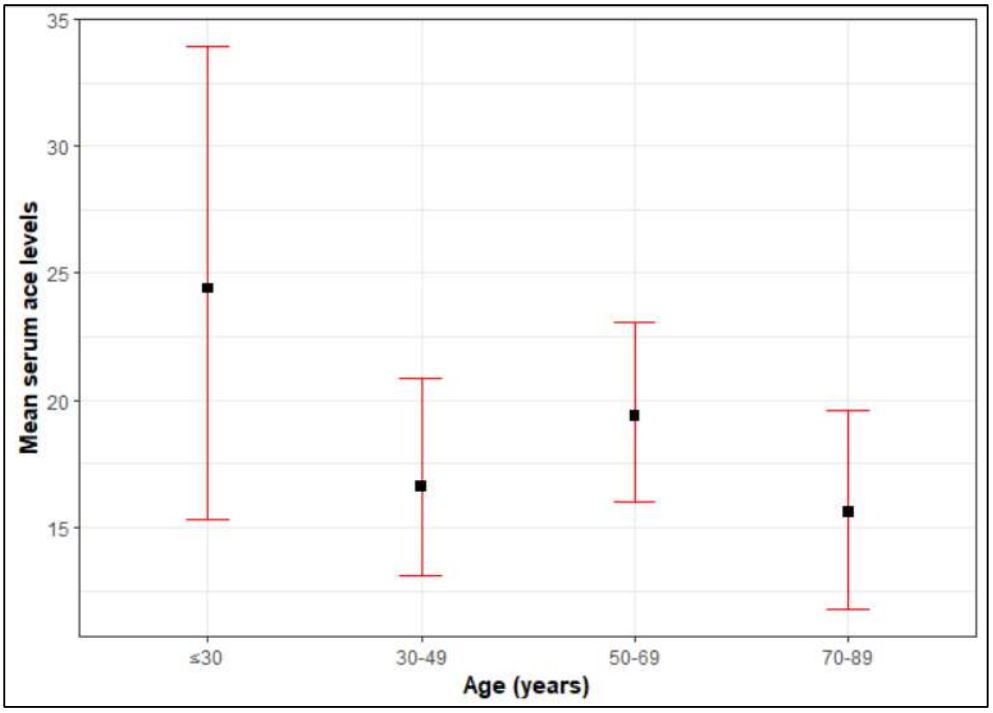

Figure 43: Mean plot of serum ace levels over age.

In mean plot of serum ace levels over age, the bars overlap on each other indicating that there is no significant difference in distribution of serum ace levels over age.

The following table gives the comparison of serum ace levels over gender.

Table 12: Comparison of serum ace levels over gender.

Gender	Serum Ace levels		p-value
	Mean ± SD	Median (Min, Max)	
Female	20.69 ± 12.03	16 (5, 55)	0.2124^{MW}
Male	17.23 ± 11.66	16 (5, 69)	

Abbreviation: MW – Mann Whitney U test.

From Mann Whitney U test, it is observed that, there is no significant difference in the distribution of serum ace levels over gender.

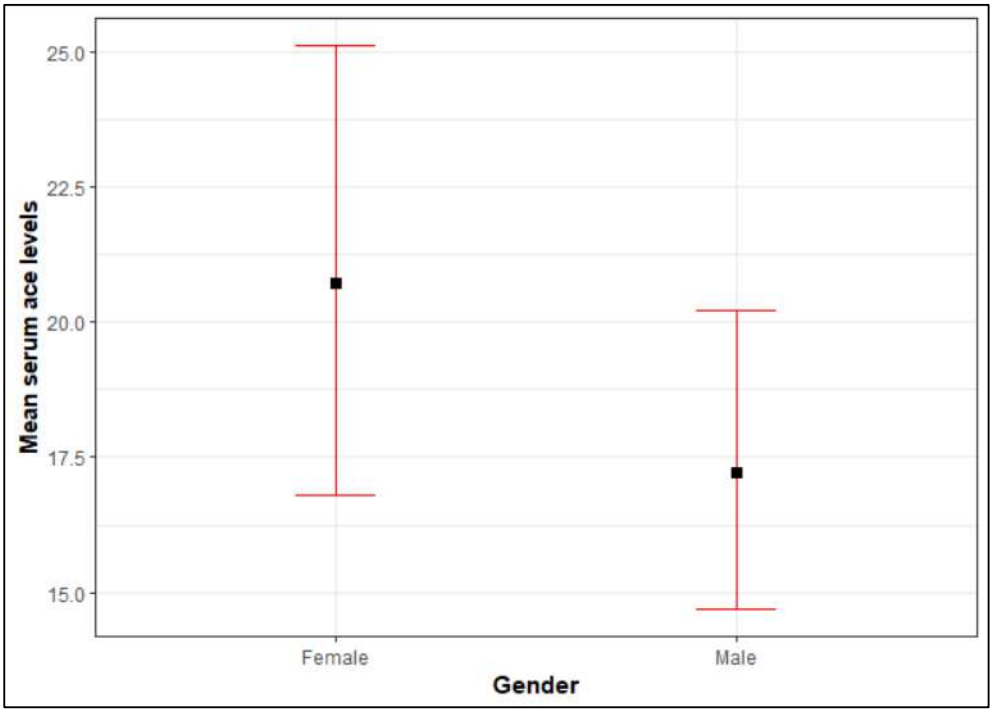

Figure 44: Mean plot of serum ace levels over gender.

In mean plot of serum ace levels over gender, the bars overlap on each other indicating that there is no significant difference in distribution of serum ace levels over gender.

DISCUSSION

COVID-19 disease is a rapidly spreading infectious disease with various disease related complications. It is well known that ACE2 is an important host cell receptor of SARS-CoV-2 that plays a crucial role in the virus entry [1]. While ACE2 are mainly expressed by the epithelial cells of various organs, excessive expression is suggestive of increased susceptibility to infection. Further, ACE2 activity has been considered as a potential biomarker for cardiac diseases. Considering higher incidence of pneumonia and bronchitis in patients with COVID-19 having high ACE levels, recently a correlation between circulating ACE levels and COVID-19 infection has been established [2]. In view of this, the present study was conducted to evaluate the serum ACE levels as a possible biomarker in COVID-19 patients.

Based on the previous studies by Zhou F, et al [3], Liu K, et al [4], Huang C, et al [5], Cao J, et al [6] and Giacomelli A, et al [7] Mortality rate of COVID-19 ranges from 11.7% to 28.2%. The variation in mortality rates in different studies could be attributed to factors including heterogeneity of study population, time of consultation, variation in treatment protocols and availability of resources. In our study, among the 101 patients included in the study, improvement was noted in 86 patients while 15 patients succumbed with a mortality rate of 14.9%. This is well within the range reported by previous studies. In our study, patients belonged to the age range of 19 to 88 years. The mean age of patients was 52.28 ± 14.55 years. The age distribution in our study is consistent with previous reports Wang D, et al [8] and Baloch S, et al [9]. Previous studies have reported increased mortality with increasing age which is related to higher incidence of comorbidities and compromised immune status in elderly patients. In accordance with the previous studies, mean age of

expired patients was significantly higher than improved patients (59.67 years vs 50.99 years; p=0.0324).

Prevalence of COVID-19 is higher in males than females and males are at higher risk of complications and mortality than females [10, 11]. Similarly, 68.3% of patients in our study were males and 31.7% were females with a gender ratio of 2.16:1. However, we did not observe a significant difference in the COVID-19 disease outcome between genders (p>0.05). In COVID-19 patients, Fever is the most common clinical manifestation. Other features include, dry cough, myalgia, dyspnea, diarrhea, abdominal pain, vomiting/nausea. Anosmia or hyposmia and loss of taste are typical features of COVID-19 and is seen in approximately 80% of patients [12, 13]. Similarly, fever was the most common complaint in our study (58.4%) followed by breathlessness (40.59%) and cough (30.69%). Frequency of patients with breathlessness was significantly higher among expired patients as compared to patients with an improvement (66.7% vs 36.1%; p=0.0259). Expired patients had 3.5 times more odds of experiencing breathlessness than patients with improvement. No difference in other clinical features was noted between expired and improved patients (p>0.05).

Presence of comorbidities are associated with poor outcome in COVID-19 patients. Reindl-Schwaighofer et al [14] reported a positive correlation between diabetes mellitus and COVID-19 patients. In our study, 12.9% patients had history of T2DM, 10.9% were hypertensives, 2.97% had thyroid disease and 1 patient had lymphoma. We did not observe any significant effect of comorbidities on COVID-19 outcome. This could be related to very low number of patients with comorbidities in our study, the lower sample size would have affected the sub-analysis.

Pulse rate was significantly higher among expired patients than improved patients (99.87 beats per minute vs 89.5 beats per minute). No difference in the mean SBP and DBP between expired and improved patients were noted. SARS-CoV-2 is primarily a respiratory pathogen which affects the lung and its functions. Decreased oxygen saturation levels, lower respiratory rate, and decreased oxygen saturation and fraction of inhaled oxygen ratio are indicative of disease progression and severity. [15, 16]. Among these parameters we evaluated the oxygen saturation levels in our study. The mean oxygen saturation levels were lower in expired patients than improved (77.6 vs 86.3), however the difference was not statistically significant.

Laboratory changes in COVID-19 disease which can be considered indicators f severity and disease outcome include heamtological markers such as decreased platelet count, lymphocyte count, hemoglobin, eosinophil count and basophil count; and elevated NLR ratio; Inflammatory markers such as elevated C reactive protein, erythrocyte sedimentation rate, Serum Ferritin, D-Dimer, Lactose dehydrogenase, cytokines and chemokines; Coagulation markers such as, increased levels of thrombin-antithrombin complex, α2-plasmininhibitor-plasmin Complex, thrombomodulin, t-PA/PAI-1 Complex, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen and thrombin time (TT); and biochemical markers such as increased levels of creatine kinase, myoglobin, aspartate aminotransferase and alanine aminotransferase, procalcitonin, reduced albumin-globulin ratio, lactose dehydrogenase, glycosuria, proteinuria, and Creatine phosphokinase levels [17-21].

In accordance with the above literature, we observed significantly lower mean hemoglobin levels among patients who expired than patients with improvement (11.6 vs 12.8; p=0.0201). However, the mean platelet count, ESR levels were comparable

between COVID-19 outcomes. Other laboratory indices such as mean D-dimer levels (2751.8 vs 1110.18; p<0.001), mean interleukin 6 (256.4 vs 90.2; p=0.0065) and mean Hs Reactive protein (160.57 vs 98.97; p=0.0039) were significantly higher among expired patients compared to improved patients. On the other hand, mean serum albumin levels were significantly lower among expired patients than improved patients (3.4 vs 3.78; p=0.0057). Other evaluated laboratory markers such as mean serum ACE levels, total bilirubin, direct bilirubin, SGOT, SGPT, alkaline phosphatase, urea, creatinine were comparable between expired and improved patients (p>0.05).

Severity of COVID-19 can also be assessed based on CT findings. The hallmark of COVID-19 is multiple, bilateral, posterior and peripheral ground glass opacities on chest CT. In severe cases these are accompanied by infiltrating shadows [17]. Based on Ct findings COVID-19 can be categorised as mild, moderate and severe disease [22]. In our study, no significant difference in the CT severity score was observed between expired and improved patients. Overall, half the patients were categorised as moderate severity, one third were categorised as severe disease and only 17% had mild disease. CT severity score was not related to disease outcome in our study. We compared the effect of different parameters and CT severity. Significant difference in the pulse rate between patients with different disease severity were noted. However, none of the other laboratory indicators had an effect on CT severity categorization.

Previous studies have suggested that monitoring ACE2 could be beneficial in assessing the disease severity and prognosis of COVID-19. They reported increased mortality risk with patients with higher ACE levels [23]. Fagyas et al [24] reported higher levels of serum ACE levels with increasing disease severity as compared to

patients without disease. Mean serum ACE levels in our study was 18.33 and was comparable between patients with improved and expired patients. In our study, the odds ratio of serum ACE levels at predicting disease outcome was 1.0 suggesting no effect. Similarly, the AUC for serum ace level is found to be 0.5609 (95% CI: 0.3923-0.7294) in predicting mortality outcome. These results confirmed that serum ACE levels is not a good predictor for mortality outcome. We further evaluated the association between CT severity score and serum ACE levels and found no significant association between serum ACE levels and CT severity. We observed a significant negative correlation between haemoglobin and serum ACE levels and significant positive correlation between Alkaline phosphatase and serum ACE levels. No correlation between other laboratory indicators and serum ACE levels was observed in our study.

CONCLUSION

In our study cohort, serum ACE levels between patients with different disease severities based on CT score and disease outcome were comparable. Further, results of our study suggested that serum ACE levels is not a good predictor for mortality outcome. Screening of serum ACE levels may be beneficial in assessing the susceptibility and severity of COVID-19 patients. We further suggest prospective, multicenter studies to evaluate the relationship between serum ACE levels and COVID-19 disease severity and clinical outcome.

SUMMARY

The present cross-sectional study was conducted at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi with an aim to evaluate whether serum ACE levels can be used as a possible biomarker in COVID-19 patients. A total of 101 adult patients >18 years of age with a confirmed diagnosis of COVID-19 were included in the study. Patients with comorbidities such as hyper- and hypothyroidism, miliary tuberculosis, asthma, COPD, Sarcoidosis and chronic liver disease were excluded.

After obtaining the ethics clearance and patient informed consent, data on age, gender, primary complaints, prior history, were recorded. Patients were categorised into severity based on CT severity score. Clinical parameters such as pulse rate, systolic and diastolic blood pressure, oxygen saturation; Laboratory parameters including hemoglobin, total leucocyte count, platelet count, ESR, D-dimer, IL-6, Hs-reactive protein, serum ACE levels, total bilirubin, direct bilirubin, SGOT, alkaline phosphatase, Serum albumin, Urea, Creatinine were recorded.

Data was analysed using statistical software R version 4.2.1 and Microsoft Excel. Two sample t test is used to compare means of variables over outcome. Mann Whitney U test is used to compare the distribution of variables over outcome. Applicability of serum ace levels to predict outcome is checked by Logistic regression. Kruskal Wallis test is used to compare the distribution of variables over CT severity score. Spearman's rank correlation test is used to check the correlation of different variables with serum ace levels. P-value less than or equal to 0.05 indicates statistical significance.

The study population consisted of 101 patients with age ranging from 19 to 88 years (mean age 52.28 years). 68.3% of patients in our study were males and 31.7%

were females with a gender ratio of 2.16:1. Overall, 85.15% patients improved, 14.85% patients succumbed. In our study, mean age of expired patients was significantly higher than improved patients (59.67 years vs 50.99 years; p=0.0324). disease outcome was comparable between genders (p>0.05).

Fever was the most common complaint in our study (58.4%) followed by breathlessness (40.59%) and cough (30.69%). Frequency of patients with breathlessness was significantly higher among expired patients vs improved patients (66.7% vs 36.1%; p=0.0259). No difference in other clinical features was noted between expired and improved patients (p>0.05). In our study, 12.9% patients had history of T2DM, 10.9% were hypertensives, 2.97% had thyroid disease and 1 patient had lymphoma. We did not observe any significant effect of comorbidities on COVID-19 outcome.

Pulse rate was significantly higher among expired patients than improved patients (99.87 beats per minute vs 89.5 beats per minute; p=0.0212). No difference in the mean SBP and DBP between expired and improved patients were noted. The mean oxygen saturation levels were lower in expired patients than improved (77.6 vs 86.3; p=0.7851). Mean hemoglobin levels was significantly lower in expired patients vs improved patients (11.6 vs 12.8; p=0.0201). However, the mean platelet count, ESR levels were comparable between COVID-19 outcomes (p>0.05).

Other laboratory indices such as mean D-dimer levels (2751.8 vs 1110.18; p<0.001), mean interleukin 6 (256.4 vs 90.2; p=0.0065) and mean Hs Reactive protein (160.57 vs 98.97; p=0.0039) were significantly higher among expired patients compared to improved patients. Conversely, mean serum albumin levels were significantly lower among expired patients than improved patients (3.4 vs 3.78; p=0.0057). Other evaluated laboratory markers such as mean serum ACE levels, total

bilirubin, direct bilirubin, SGOT, SGPT, alkaline phosphatase, urea, creatinine were comparable between expired and improved patients ($p>0.05$).

Mean CT severity score was comparable between expired and improved patients (13.4 vs 13.23; $p=0.9084$). Overall, 49.5% were categorised as moderate severity, 33.6% had severe disease and only 17% had mild disease. CT severity score was not related to disease outcome in our study. Significant difference in the pulse rate between patients with different disease severity were noted ($p=0.0484$). However, none of the other laboratory indicators had an effect on CT severity categorization ($p>0.05$).

Mean serum ACE levels in our study was 18.33 and was comparable between patients with improved and expired patients. In our study, the odds ratio of serum ACE levels at predicting disease outcome was 1.0 suggesting no effect. Similarly, the AUC for serum ace level is found to be 0.5609 (95% CI: 0.3923-0.7294) in predicting mortality outcome. No significant association between serum ACE levels and CT severity. We observed a significant negative correlation between haemoglobin and serum ACE levels and significant positive correlation between Alkaline phosphatase and serum ACE levels.

Limitations of the study

- Single center study
- Cross sectional nature of the study with its inherent limitations
- Relatively smaller sample size

Future perspectives

Although we did not observe a significant relationship between ACE levels with disease severity based on CT score and disease outcome among COVID-19 patients, further prospective, multicenter studies are warranted to evaluate this relationship.

BIBLIOGRAPHY

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020 Feb 15;395(10223):497-506.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P. A novel coronavirus from patients with pneumonia in China, 2019. New England journal of medicine. 2020 Jan 24.
3. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD. A pneumonia outbreak associated with a new coronavirus of probable bat origin. nature. 2020 Mar;579(7798):270-3.
4. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE. A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circulation research. 2000 Sep 1;87(5):e1-9.
5. Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomedicine & Pharmacotherapy. 2017 Oct 1;94:317-25.
6. Santos RA, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, Campagnole-Santos MJ. The ACE2/angiotensin-(1–7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1–7). Physiological reviews. 2017 Dec 20.
7. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis GV, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology: A

Journal of the Pathological Society of Great Britain and Ireland. 2004 Jun;203(2):631-7.

8. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020 Apr 16;181(2):271-80.
9. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Mar 13;367(6483):1260-3.
10. Wang LS, Wang YR, Ye DW, et al. Review of the 2019 novel coronavirus (COVID-19) based on current evidence. Int J Antimicrob Agents 2020; 55: 1059.
11. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, Talavera-López C, Maatz H, Reichart D, Sampaziotis F, Worlock KB. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nature medicine. 2020 May;26(5):681-7.
12. Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, Bolling MC, Dijkstra G, Voors AA, Osterhaus AD, van Der Voort PH. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). The Journal of pathology. 2020 Jul;251(3):228-48.
13. https://www.apollodiagnostics.in/test/angiotensin-converting-enzyme-ace.
14. Santos RA, Ferreira AJ, Verano-Braga T, Bader M. Angiotensin-converting enzyme 2, angiotensin-(1-7) and Mas: new players of the renin-angiotensin system. J endocrinol. 2013 Jan 18;216(2):R1-7.

15. Ferrario CM, Trask AJ, Jessup JA. Advances in biochemical and functional roles of angiotensin-converting enzyme 2 and angiotensin-(1–7) in regulation of cardiovascular function. American Journal of Physiology-Heart and Circulatory Physiology. 2005 Dec;289(6):H2281-90.

16. Campbell DJ, Zeitz CJ, Esler MD, Horowitz JD. Evidence against a major role for angiotensin converting enzyme-related carboxypeptidase (ACE2) in angiotensin peptide metabolism in the human coronary circulation. Journal of Hypertension. 2004 Oct 1;22(10):1971-6.

17. Petty WJ, Miller AA, McCoy TP, Gallagher PE, Tallant EA, Torti FM. Phase I and pharmacokinetic study of angiotensin-(1-7), an endogenous antiangiogenic hormone. Clinical Cancer Research. 2009 Dec 1;15(23):7398-404.

18. Voors AA, Pinto YM, Buikema H, Urata H, Oosterga M, Rooks G, Grandjean JG, Ganten D, Van Gilst WH. Dual pathway for angiotensin II formation in human internal mammary arteries. British journal of pharmacology. 1998 Nov;125(5):1028-32.

19. Ferrario CM, Trask AJ, Jessup JA. Advances in biochemical and functional roles of angiotensin-converting enzyme 2 and angiotensin-(1–7) in regulation of cardiovascular function. American Journal of Physiology-Heart and Circulatory Physiology. 2005 Dec;289(6):H2281-90.

20. Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. International journal of peptides. 2012;2012.

21. Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. Angiotensin-converting enzyme 2 and antihypertensives (angiotensin receptor blockers and

angiotensin-converting enzyme inhibitors) in coronavirus disease 2019. InMayo Clinic Proceedings 2020 Jun 1 (Vol. 95, No. 6, pp. 1222-1230). Elsevier.

22. Hamming I, Cooper ME, Haagmans BL, Hooper NM, Korstanje R, Osterhaus AD, Timens W, Turner AJ, Navis G, van Goor H. The emerging role of ACE2 in physiology and disease. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. 2007 May;212(1):1-1.
23. Bernardi S, Toffoli B, Zennaro C, Tikellis C, Monticone S, Losurdo P, Bellini G, Thomas MC, Fallo F, Veglio F, Johnston CI. High-salt diet increases glomerular ACE/ACE2 ratio leading to oxidative stress and kidney damage. Nephrology Dialysis Transplantation. 2012 May 1;27(5):1793-800.
24. Gupte M, Boustany-Kari CM, Bharadwaj K, Police S, Thatcher S, Gong MC, English VL, Cassis LA. ACE2 is expressed in mouse adipocytes and regulated by a high-fat diet. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2008 Sep;295(3):R781-8.
25. Hernández-Díazcouder A, Romero-Nava R, Carbó R, Sánchez-Lozada LG, Sánchez-Muñoz F. High fructose intake and adipogenesis. International journal of molecular sciences. 2019 Jun 7;20(11):2787.
26. Hamming I, Van Goor H, Turner AJ, Rushworth CA, Michaud AA, Corvol P, Navis G. Differential regulation of renal angiotensin-converting enzyme (ACE) and ACE2 during ACE inhibition and dietary sodium restriction in healthy rats. Experimental physiology. 2008 May 1;93(5):631-8.
27. van de Veerdonk F, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Bruggemann RJ, van der Hoeven H. Kinins and cytokines in COVID-19: a comprehensive pathophysiological approach 2020.

28. Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, Sigl V, Hanada T, Hanada R, Lipinski S, Wild B. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature. 2012 Jul;487(7408):477-81.

29. Lely AT, Hamming I, van Goor H, Navis GJ. Renal ACE2 expression in human kidney disease. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. 2004 Dec;204(5):587-93.

30. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003 Nov;426(6965):450-4.

31. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nature medicine. 2005 Aug;11(8):875-9.

32. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005 Jul;436(7047):112-6.

33. Li Y, Zeng Z, Cao Y, Liu Y, Ping F, Liang M, Xue Y, Xi C, Zhou M, Jiang W. Angiotensin-converting enzyme 2 prevents lipopolysaccharide-induced rat acute lung injury via suppressing the ERK1/2 and NF-κB signaling pathways. Scientific reports. 2016 Jun 15;6(1):1-4.

34. Ye R, Liu Z. ACE2 exhibits protective effects against LPS-induced acute lung injury in mice by inhibiting the LPS-TLR4 pathway. Experimental and molecular pathology. 2020 Apr 1;113:104350.

35. Yang XH, Deng W, Tong Z, Liu YX, Zhang LF, Zhu H, Gao H, Huang L, Liu YL, Ma CM, Xu YF. Mice transgenic for human angiotensin-converting enzyme 2 provide a model for SARS coronavirus infection. Comparative medicine. 2007 Oct 1;57(5):450-9.

36. Gaur P, Saini S, Vats P, Kumar B. Regulation, signalling and functions of hormonal peptides in pulmonary vascular remodelling during hypoxia. Endocrine. 2018 Mar;59(3):466-80.

37. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, Hou C, Wang H, Liu J, Yang D, Xu Y. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Critical Care. 2020 Dec;24(1):1-0.

38. 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.

39. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. Journal of virology. 2020 Mar 17;94(7):e00127-20.

40. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nature medicine. 2005 Aug;11(8):875-9.

41. Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. Pharmacological research. 2017 Nov 1;125:21-38.

42. Rodriguez GE, Shin BC, Abernathy RS, Kendig Jr EL. Serum angiotensin-converting enzyme activity in normal children and in those with sarcoidosis. The Journal of pediatrics. 1981 Jul 1;99(1):68-72.

43. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020 Apr 16;181(2):271-80.

44. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive care medicine. 2020 Apr;46(4):586-90.

45. Zoufaly A, Poglitsch M, Aberle JH, Hoepler W, Seitz T, Traugott M, Grieb A, Pawelka E, Laferl H, Wenisch C, Neuhold S. Human recombinant soluble ACE2 in severe COVID-19. The Lancet Respiratory Medicine. 2020 Nov 1;8(11):1154-8.

46. Tong M, Jiang Y, Xia D, Xiong Y, Zheng Q, Chen F, Zou L, Xiao W, Zhu Y. Elevated expression of serum endothelial cell adhesion molecules in COVID-19 patients. The Journal of infectious diseases. 2020 Aug 17;222(6):894-8.

47. Escher R, Breakey N, Lämmle B. Severe COVID-19 infection associated with endothelial activation. Thrombosis research. 2020 Jun 1;190:62.

48. Garvin MR, Alvarez C, Miller JI, Prates ET, Walker AM, Amos BK, Mast AE, Justice A, Aronow B, Jacobson D. A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. elife. 2020 Jul 7;9:e59177.

49. Vickers C, Hales P, Kaushik V, Dick L, Gavin J, Tang J, Godbout K, Parsons T, Baronas E, Hsieh F, Acton S. Hydrolysis of biological peptides by human

angiotensin-converting enzyme-related carboxypeptidase. Journal of Biological Chemistry. 2002 Apr 26;277(17):14838-43.

50. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. pii: S0092-8674 (20) 30262-2.

51. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020 Apr 16;181(2):271-80.

52. Matsuyama S, Nao N, Shirato K, Kawase M, Saito S, Takayama I, Nagata N, Sekizuka T, Katoh H, Kato F, Sakata M. Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proceedings of the National Academy of Sciences. 2020 Mar 31;117(13):7001-3.

53. Tortorici MA, Walls AC, Lang Y, Wang C, Li Z, Koerhuis D, Boons GJ, Bosch BJ, Rey FA, de Groot RJ, Veesler D. Structural basis for human coronavirus attachment to sialic acid receptors. Nature structural & molecular biology. 2019 Jun;26(6):481-9.

54. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, Liu C, Yang C. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain, behavior, and immunity. 2020 Jul 1;87:18-22.

55. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. New England Journal of Medicine. 2020 Jul 9;383(2):120-8.

56. Kam YW, Okumura Y, Kido H, Ng LF, Bruzzone R, Altmeyer R. Cleavage of the SARS coronavirus spike glycoprotein by airway proteases enhances virus entry into human bronchial epithelial cells in vitro. PloS one. 2009 Nov 17;4(11):e7870.

57. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020 May;581(7807):221-4.

58. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacologica Sinica. 2020 Sep;41(9):1141-9.

59. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen KY, Wang Q. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell. 2020 May 14;181(4):894-904.

60. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, Li F. Cell entry mechanisms of SARS-CoV-2. Proceedings of the National Academy of Sciences. 2020 May 26;117(21):11727-34.

61. Xia S, Lan Q, Su S, Wang X, Xu W, Liu Z, Zhu Y, Wang Q, Lu L, Jiang S. The role of furin cleavage site in SARS-CoV-2 spike protein-mediated membrane fusion in the presence or absence of trypsin. Signal transduction and targeted therapy. 2020 Jun 12;5(1):1-3.

62. Coutard B, Valle C, De Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral research. 2020 Apr 1;176:104742.

63. Kearney J. Chloroquine as a potential treatment and prevention measure for the 2019 novel coronavirus: a review.

64. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020 Mar 27;367(6485):1444-8.

65. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. Journal of pharmaceutical analysis. 2020 Apr 1;10(2):102-8.

66. Busse LW, Chow JH, McCurdy MT, Khanna AK. COVID-19 and the RAAS—a potential role for angiotensin II?. Critical Care. 2020 Dec;24(1):1-4.

67. Guo J, Huang Z, Lin L, Lv J. Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. Journal of the American Heart Association. 2020 Apr 9;9(7):e016219.

68. Triana S, Metz-Zumaran C, Ramirez C, Kee C, Doldan P, Shahraz M, Schraivogel D, Gschwind AR, Sharma AK, Steinmetz LM, Herrmann C. Single-cell analyses reveal SARS-CoV-2 interference with intrinsic immune response in the human gut. Molecular systems biology. 2021 Apr;17(4):e10232.

69. Seltzer S. Linking ACE2 and angiotensin II to pulmonary immunovascular dysregulation in SARS-CoV-2 infection. International Journal of Infectious Diseases. 2020 Dec 1;101:42-5.

70. Hofmann H, Geier M, Marzi A, Krumbiegel M, Peipp M, Fey GH, Gramberg T, Pöhlmann S. Susceptibility to SARS coronavirus S protein-driven infection correlates with expression of angiotensin converting enzyme 2 and infection can

be blocked by soluble receptor. Biochemical and biophysical research communications. 2004 Jul 9;319(4):1216-21.

71. Ashour HM, Elkhatib WF, Rahman MM, Elshabrawy HA. Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks. Pathogens. 2020 Mar 4;9(3):186.

72. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Is COVID-19 an endothelial disease? Clinical and basic evidence.2020.

73. Ren X, Glende J, Al-Falah M, de Vries V, Schwegmann-Wessels C, Qu X, Tan L, Tschernig T, Deng H, Naim HY, Herrler G. Analysis of ACE2 in polarized epithelial cells: surface expression and function as receptor for severe acute respiratory syndrome-associated coronavirus. Journal of general virology. 2006 Jun 1;87(6):1691-5.

74. Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2007 Jan;292(1):R373-81.

75. Gembardt F, Sterner-Kock A, Imboden H, Spalteholz M, Reibitz F, Schultheiss HP, Siems WE, Walther T. Organ-specific distribution of ACE2 mRNA and correlating peptidase activity in rodents. Peptides. 2005 Jul 1;26(7):1270-7.

76. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis GV, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. 2004 Jun;203(2):631-7.

77. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS letters. 2002 Dec 4;532(1-2):107-10.

78. Patel VB, Clarke N, Wang Z, Fan D, Parajuli N, Basu R, Putko B, Kassiri Z, Turner AJ, Oudit GY. Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. Journal of molecular and cellular cardiology. 2014 Jan 1;66:167-76.

79. Serfozo P, Wysocki J, Gulua G, Schulze A, Ye M, Liu P, Jin J, Bader M, Myöhänen T, García-Horsman JA, Batlle D. Ang II (angiotensin II) conversion to angiotensin-(1-7) in the circulation is POP (prolyloligopeptidase)-dependent and ACE2 (angiotensin-converting enzyme 2)-independent. Hypertension. 2020 Jan;75(1):173-82.

80. Warner FJ, Lew RA, Smith AI, Lambert DW, Hooper NM, Turner AJ. Angiotensin-converting enzyme 2 (ACE2), but not ACE, is preferentially localized to the apical surface of polarized kidney cells. Journal of Biological Chemistry. 2005 Nov 25;280(47):39353-62.

81. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE. A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circulation research. 2000 Sep 1;87(5):e1-9.

82. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme: cloning and functional expression as a captopril-insensitive carboxypeptidase. Journal of Biological Chemistry. 2000 Oct 27;275(43):33238-43.

83. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension. 2004 May 1;43(5):970-6.

84. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochemical Journal. 2004 Oct 1;383(1):45-51.

85. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB, Oudit GY. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circulation research. 2020 May 8;126(10):1456-74.

86. Fountain JH, Lappin SL. Physiology, renin angiotensin system.2017.

87. Kopf PG, Campbell WB. Endothelial metabolism of angiotensin II to angiotensin III, not angiotensin (1–7), augments the vasorelaxation response in adrenal cortical arteries. Endocrinology. 2013 Dec 1;154(12):4768-76.

88. Al-Merani SA, Brooks DP, Chapman BJ, Munday KA. The half-lives of angiotensin II, angiotensin II-amide, angiotensin III, Sar1-Ala8-angiotensin II and renin in the circulatory system of the rat. The Journal of physiology. 1978 May 1;278(1):471-90.

89. Zhuo J, Moeller I, Jenkins T, Chai SY, Allen AM, Ohishi M, Mendelsohn FA. Mapping tissue angiotensin-converting enzyme and angiotensin AT1, AT2 and AT4 receptors. Journal of hypertension. 1998 Dec 1;16(12):2027-37.

90. Dasgupta C, Zhang L. Angiotensin II receptors and drug discovery in cardiovascular disease. Drug discovery today. 2011 Jan 1;16(1-2):22-34.

91. Gohla A, Schultz G, Offermanns S. Role for G12/G13 in agonist-induced vascular smooth muscle cell contraction. Circulation research. 2000 Aug 4;87(3):221-7.

92. Castrén E, Kurihara M, Gutkind JS, Saavedra JM. Specific angiotensin II binding sites in the rat stellate and superior cervical ganglia. Brain research. 1987 Oct 6;422(2):347-51.

93. Foster RH, MacFarlane CH, Bustamante MO. Recent progress in understanding aldosterone secretion. General Pharmacology: The Vascular System. 1997 May 1;28(5):647-51.

94. Katada J, Majima M. AT2 receptor-dependent vasodilation is mediated by activation of vascular kinin generation under flow conditions. British journal of pharmacology. 2002 Jun;136(4):484-91.

95. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, McDowell C, Laffey JG, O'Kane CM, McAuley DF, Johnston AJ. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. The Lancet Respiratory Medicine. 2018 Sep 1;6(9):691-8.

96. Wada T, Jesmin S, Gando S, Yanagida Y, Mizugaki A, Sultana SN, Zaedi S, Yokota H. The role of angiogenic factors and their soluble receptors in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) associated with critical illness. Journal of inflammation. 2013 Dec;10(1):1-8.

97. Akwii RG, Sajib MS, Zahra FT, Mikelis CM. Role of angiopoietin-2 in vascular physiology and pathophysiology. Cells. 2019 May 17;8(5):471.

98. Liu Y, Cox SR, Morita T, Kourembanas S. Hypoxia regulates vascular endothelial growth factor gene expression in endothelial cells: identification of a 5′ enhancer. Circulation research. 1995 Sep 1;77(3):638-43.

99. Chen XL, Nam JO, Jean C, Lawson C, Walsh CT, Goka E, Lim ST, Tomar A, Tancioni I, Uryu S, Guan JL. VEGF-induced vascular permeability is mediated by FAK. Developmental cell. 2012 Jan 17;22(1):146-57.

100. Wu Z, Hu R, Zhang C, Ren W, Yu A, Zhou X. Elevation of plasma angiotensin II level is a potential pathogenesis for the critically ill COVID-19 patients. Critical Care. 2020 Dec;24(1):1-3.

101. Simões e Silva AC, Silveira KD, Ferreira AJ, Teixeira MM. ACE2, angiotensin-(1-7) and M as receptor axis in inflammation and fibrosis. British journal of pharmacology. 2013 Jun;169(3):477-92.

102. Magalhaes GS, Rodrigues-Machado MD, Motta-Santos D, Campagnole-Santos MJ, Santos RA. Activation of Ang-(1-7)/Mas receptor is a possible strategy to treat coronavirus (SARS-CoV-2) infection. Frontiers in Physiology. 2020 Jun 19;11:730.

103. Erdös EG, Jackman HL, Brovkovych V, Tan F, Deddish PA. Products of angiotensin I hydrolysis by human cardiac enzymes potentiate bradykinin. Journal of molecular and cellular cardiology. 2002 Dec 1;34(12):1569-76.

104. Bruce E, Shenoy V, Rathinasabapathy A, Espejo A, Horowitz A, Oswalt A, Francis J, Nair A, Unger T, Raizada MK, Steckelings UM. Selective activation of angiotensin AT 2 receptors attenuates progression of pulmonary hypertension and inhibits cardiopulmonary fibrosis. British Journal of Pharmacology. 2015 May;172(9):2219-31.

105. Ocaranza MP, Jalil JE. Protective role of the ACE2/Ang-(1–9) axis in cardiovascular remodeling. International journal of hypertension. 2012 Oct;2012.

106. Ocaranza MP, Lavandero S, Jalil JE, Moya J, Pinto M, Novoa U, Apablaza F, Gonzalez L, Hernandez C, Varas M, Lopez R. Angiotensin-(1–9) regulates cardiac hypertrophy in vivo and in vitro. Journal of hypertension. 2010 May 1;28(5):1054-64.

107. Ocaranza MP, Moya J, Barrientos V, Alzamora R, Hevia D, Morales C, Pinto M, Escudero N, García L, Novoa U, Ayala P. Angiotensin-(1–9) reverses experimental hypertension and cardiovascular damage by inhibition of the angiotensin converting enzyme/Ang II axis. Journal of hypertension. 2014 Apr 1;32(4):771-83.

108. Jackman HL, Massad MG, Sekosan M, Tan F, Brovkovych V, Marcic BM, Erdös EG. Angiotensin 1-9 and 1-7 release in human heart: role of cathepsin A. Hypertension. 2002 May 1;39(5):976-81.

109. Flores-Munoz M, Work LM, Douglas K, Denby L, Dominiczak AF, Graham D, Nicklin SA. Angiotensin-(1-9) attenuates cardiac fibrosis in the stroke-prone spontaneously hypertensive rat via the angiotensin type 2 receptor. Hypertension. 2012 Feb;59(2):300-7.

110. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. The Lancet Respiratory Medicine. 2020 Aug 1;8(8):807-15.

111. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z. Clinical and biochemical indexes from 2019-nCoV infected

patients linked to viral loads and lung injury. Science China Life Sciences. 2020 Mar;63(3):364-74.

112. Tawinwung S, Petpiroon N, Chanvorachote P. Blocking of type 1 angiotensin II receptor inhibits T-lymphocyte activation and IL-2 production. in vivo. 2018 Nov 1;32(6):1353-9.

113. Ross SH, Cantrell DA. Signaling and function of interleukin-2 in T lymphocytes. Annual review of immunology. 2018 Apr 26;36:411.

114. Samprathi M, Jayashree M. Biomarkers in COVID-19: an up-to-date review. Frontiers in pediatrics. 2021 Mar 30;8:607647.

115. Butler-Laporte G, Nakanishi T, Mooser V, Renieri A, Amitrano S, Zhou S, Chen Y, Forgetta V, Richards JB. The effect of angiotensin-converting enzyme levels on COVID-19 susceptibility and severity: a Mendelian randomization study. International journal of epidemiology. 2021 Feb;50(1):75-86.

116. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020 Mar 17;323(11):1061-9.

117. Fagyas M, Fejes Z, Sütő R, Nagy Z, Székely B, Pócsi M, Ivády G, Bíró E, Bekő G, Nagy A, Kerekes G. Circulating ACE2 activity predicts mortality and disease severity in hospitalized COVID-19 patients. International Journal of Infectious Diseases. 2022 Feb 1;115:8-16.

118. Liang W, Yao J, Chen A, Lv Q, Zanin M, Liu J, Wong S, Li Y, Lu J, Liang H, Chen G. Early triage of critically ill COVID-19 patients using deep learning. Nature communications. 2020 Jul 15;11(1):1-7.

119. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, Gao G. The potential role of serum angiotensin-converting enzyme in coronavirus disease 2019. BMC Infectious Diseases. 2020 Dec;20(1):1-8.

120. Kragstrup TW, Singh HS, Grundberg I, Nielsen AL, Rivellese F, Mehta A, Goldberg MB, Filbin MR, Qvist P, Bibby BM. Plasma ACE2 predicts outcome of COVID-19 in hospitalized patients. PloS one. 2021 Jun 4;16(6):e0252799.

121. Chen Y, Huang D, Yuan W, Chang J, Yuan Z, Wu D, Han M, Luo X, Ning Q, Yan W. Lower serum angiotensin-converting enzyme level in relation to hyperinflammation and impaired antiviral immune response contributes to progression of COVID-19 infection. Infectious Diseases and Therapy. 2021 Dec;10(4):2431-46.

122. Fagyas M, Fejes Z, Sütő R, Nagy Z, Székely B, Pócsi M, Ivády G, Bíró E, Bekő G, Nagy A, Kerekes G. Circulating ACE2 activity predicts mortality and disease severity in hospitalized COVID-19 patients. International Journal of Infectious Diseases. 2022 Feb 1;115:8-16.

123. Avanoglu Guler A, Tombul N, Aysert Yıldız P, Özger HS, Hızel K, Gulbahar O, Tufan A, Erbaş G, Aygencel G, Guzel Tunccan O, Dizbay M. The assessment of serum ACE activity in COVID-19 and its association with clinical features and severity of the disease. Scandinavian Journal of Clinical and Laboratory Investigation. 2021 Apr 1;81(2):160-5.

124. Assessment RR. Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK–ninth update. European Centre for Disease Prevention and Control: Stockholm. 2020 Apr 23.

125. Choices NH. Coronavirus (Covid-19). Advice for people at high risk.

126. Jordan RE, Adab P, Cheng K. Covid-19: risk factors for severe disease and death. Bmj. 2020 Mar 26;368.

127. Reindl-Schwaighofer R, Hödlmoser S, Eskandary F, Poglitsch M, Bonderman D, Strassl R, Aberle JH, Oberbauer R, Zoufaly A, Hecking M. ACE2 elevation in severe COVID-19. American journal of respiratory and critical care medicine. 2021 May 1;203(9):1191-6.

128. Scohy A, Anantharajah A, Bodéus M, Kabamba-Mukadi B, Verroken A, Rodriguez-Villalobos H. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. Journal of Clinical Virology. 2020 Aug 1;129:104455.

129. Lagolio E, Demurtas J, Buzzetti R, Cortassa G, Bottone S, Spadafora L, Cocino C, Smith L, Benzing T, Polidori MC. A rapid and feasible tool for clinical decision making in community-dwelling patients with COVID-19 and those admitted to emergency departments: The Braden-LDH-HorowITZ Assessment—BLITZ. Internal and Emergency Medicine. 2022 Apr;17(3):839-44.

130. Prasad S, Patel S, Behera AK, Gitismita N, Shah S, Nanda R, Mohapatra E. Early Biochemical Markers in Predicting the Clinical Outcome of COVID-19 Patients Admitted in Tertiary Care Hospital in Chhattisgarh, India. Journal of Laboratory Physicians. 2022 Feb 10.

131. Xu Y, Yang H, Wang J, Li X, Xue C, Niu C, Liao P. Serum albumin levels are a predictor of COVID-19 patient prognosis: Evidence from a single cohort in Chongqing, China. International journal of general medicine. 2021;14:2785.

132. Aiman S, Singla SK, Singh R. Study of biochemical markers of COVID-19 in western punjab. Int J Acad Med Pharm. 2022;4(4):577-83.

133. 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. Lancet. 2020;395(10224):565-574.

134. Ciaglia E, Vecchione C, Puca AA. COVID-19 Infection and Circulating ACE2 Levels: Protective Role in Women and Children. Front Pediatr. 2020;8:206.

135. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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(10229):1054-1062.

136. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020;133(9):1025-1031.

137. 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. 2020;395(10223):497-506.

138. Cao J, Tu WJ, Cheng W, Yu L, Liu YK, Hu X, et al. Clinical Features and Short-term Outcomes of 102 Patients with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71(15):748-755.

139. Giacomelli A, Ridolfo AL, Milazzo L, Oreni L, Bernacchia D, Siano M, et al. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: A prospective cohort study. Pharmacol Res. 2020;158:104931.

140. 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;323(11):1061-1069.

141. Baloch S, Baloch MA, Zheng T, Pei X. The Coronavirus Disease 2019 (COVID-19) Pandemic. Tohoku J Exp Med. 2020;250(4):271-278.

142. Taj S, Kashif A, Arzinda Fatima S, Imran S, Lone A, Ahmed Q. Role of hematological parameters in the stratification of COVID-19 disease severity. Ann Med Surg (Lond). 2021;62:68-72.

143. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Health. 2020;8:152.

144. 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;323(13):1239-1242.

145. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. Gastroenterology. 2020;159(1):81-95.

146. Reindl-Schwaighofer R, Hodlmoser S, Eskandary FA, Poglitsch M. Angiotensin-converting enzyme 2 (ACE2) elevation in severe COVID-19. Am J Respir Crit Care Med. 2021; 203 (9):1191-6.

147. Pan F, Yang L, Li Y, Liang B, Li L, Ye T, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study. Int J Med Sci. 2020;17(9):1281-1292.

148. Choi KJ, Hong HL, Kim EJ. The Association between Mortality and the Oxygen Saturation and Fraction of Inhaled Oxygen in Patients Requiring Oxygen Therapy due to COVID-19-Associated Pneumonia. Tuberc Respir Dis (Seoul).

2021;84(2):125-133.

149. Mohamadian M, Chiti H, Shoghli A, Biglari S, Parsamanesh N, Esmaeilzadeh A. COVID-19: Virology, biology and novel laboratory diagnosis. J Gene Med. 2021;23(2):e3303.

150. Palladino M. Complete blood count alterations in COVID-19 patients: A narrative review. Biochem Med (Zagreb). 2021;31(3):030501.

151. Umakanthan S, Sahu P, Ranade AV, Bukelo MM, Rao JS, Abrahao-Machado LF, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). Postgrad Med J. 2020;96(1142):753-758.

152. Fadaka AO, Sibuyi NRS, Adewale OB, Bakare OO, Akanbi MO, Klein A, Madiehe AM, Meyer M. Understanding the epidemiology, pathophysiology, diagnosis and management of SARS-CoV-2. J Int Med Res. 2020;48(8):300060520949077.

153. Jin X, Duan Y, Bao T, Gu J, Chen Y, Li Y, et al. The values of coagulation function in COVID-19 patients. PLoS One. 2020;15(10):e0241329.

154. Zahorec R, Hulin I, Zahorec P. Rationale Use of Neutrophil-to-lymphocyte ratio for early diagnosis and stratifi cation of COVID-19. Bratisl Med J. 2020;121(7): 466-470.

155. Kragstrup TW, Singh HS, Grundberg I, Nielsen AL, Rivellese F, Mehta A, et al. Plasma ACE2 predicts outcome of COVID-19 in hospitalized patients. PLoS One. 2021 Jun 4;16(6):e0252799.

156. Fagyas M, Fejes Z, Sütő R, Nagy Z, Székely B, Pócsi M, et al. Circulating ACE2 activity predicts mortality and disease severity in hospitalized COVID-19 patients. Int J Infect Dis. 2022 Feb;115:8-16.

ANNEXURE I

INFORMED CONSENT

Principal Investigator: -

REG NO: BG0120007

Post Graduate Student, Department of General Medicine,JNMC, Belagavi.

Guide: -

Dr. _____

REGISTRAR

Department of General Medicine,JNMC, Belagavi.

Introduction and Purpose: - The pandemic of coronavirus disease-19 (COVID-19) has been associated with substantial morbidity and mortality. The causative agent of COVID-19 hasbeen known to be severe acute respiratory syndrome coronavirus-2

(SARS-CoV-2). It is a novel enveloped ribonucleic acid (RNA) beta-coronavirus. The disease was first reported in Wuhan, Hubei Province of China, in December 2019, after a cluster of cases with unknown causes of pneumonia that did not respond to usual treatments. By the end of January 2020, the WHO declared the disease as pandemic. As of May 1, 2020, the disease had spread to 187 countries, affecting 3 crore plus population. *This study may predict the Angiotensin converting enzyme (ACE) as a possible biomarker topredict severity of covid 19 disease.

You are being asked to enroll yourself in the above said research as you are eligible for participation in this study being conducted at J N Medical College, KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi from OCTOBER 2020 to SEPTEMBER 2021 conducted by **REG NO: BG0120007** post graduate student in the Dept. of Medicine under the guidance of **Dr. _____.**

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also haveto give blood samples for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your armfor the investigations. It may cause swelling, pain, redness (rarely happens) at the site from where the blood is drawn.

You may not be benefitted by these investigations but you will be part of this study whichis going to be useful to others in the future.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study.

If you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time.If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will beconfidential in any publication.

Institution / Sponsor's policy:

Does not apply to this research

Financial incentives for participation:

No additional costs shall be incurred upon you for the purpose of this study. It is purely being done with the idea of research and all the cost of study will be borne by the investigator. You willnot be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results:

The results of the study would be forwarded to the KLE University, Belagavi as part ofrequirement towards the completion of MD degree, review and publishing.

In case of the queries during study or in future you may contact following persons,

REG NO: BG0120007

Post Graduate Student, Department of General Medicine,JNMC, Belagavi.

Dr. _____

PROFESSOR

DEPT OF GENERAL MEDICNE

J.N. MEDICAL COLLEGEBELAGAVI

Dr. HARSHA HEGDE,

CHAIRPERSON, JNMC, IEC & Scientist D,ICMR,

National Institute of Traditional Medicine,Belagavi- 9480422500

CONSENT FORM

I, voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me, this consent form and have had all the questions answered.

Name of the Participant
Signature of the participant or Left-Hand Thumb impression

Name of Investigator
Signature of investigator or Left-Hand Thumb impression

Name of Witness
Signature of Witnessor Left-Hand Thumb impression

Date:

Place:

ತಿಳುವಳಿಕೆಯ ಸಮ್ಮತಿ

" ಕೋವಿಡ್ -19 ನಲ್ಲಿ ಸೀರಮ್ ಆಂಜಿಯೋಟೆನ್ಸಿನ್ ಎಂಜೈಮ್ ಮಟ್ಟವನ್ನು ಸಂಭಾವ್ಯ ಬಯೋಮಾರ್ಕರ್ ಆಗಿ ಪರಿವರ್ತಿಸುವ ಕ್ಲಿನಿಕಲ್ ಸ್ಟಡಿ".

ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿ: - **REG NO: BG0120007**
ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿ
ಜನರಲ್ ಮೆಡಿಸಿನ್ ಇಲಾಖೆ,
ಜೆಎನ್ಎಂಸಿ, ಬೆಳಗಾವಿ.

ಮಾರ್ಗದರ್ಶಿ: _____
ರೆಜಿಸ್ಟ್ರಾರ್ ಮತ್ತು ಒಂದು ಘಟಕದ ಮುಖ್ಯಸ್ಥ
ಜನರಲ್ ಮೆಡಿಸಿನ್ ಇಲಾಖೆ,
ಜೆಎನ್ಎಂಸಿ, ಬೆಳಗಾವಿ.

ಪರಿಚಯ ಮತ್ತು ಉದ್ದೇಶ: -

ಕೊರೊನಾವೈರಸ್ ಕಾಯಿಲೆ -19 (ಕೋವಿಡ್-19) ನ ಸಾಂಕ್ರಾಮಿಕ ರೋಗವು ಗಣನೀಯ ಅಸ್ವಸ್ಥತೆ ಮತ್ತು ಮರಣಕ್ಕೆ ಸಂಬಂಧಿಸಿದೆ. ಕೋವಿಡ್ -19 ನ ಕಾರಣವಾಗುವ ಏಜೆಂಟ್ ತೀವ್ರ ಉಸಿರಾಟದ ಸಿಂಡ್ರೋಮ್ ಕೊರೊನಾವೈರಸ್ -2 (ಸಾರ್ಸ್ ಸಿ ಒ ವಿ -2) ಎಂದು ತಿಳಿದುಬಂದಿದೆ. ಇದು ಕಾದಂಬರಿ ಹೊದಿಕೆಯ ರಿಬೊನ್ಯೂಕ್ಲಿಯಿಕ್ ಆಮ್ಲ (ಆರ್ ಎನ್ ಎ) ಬೀಟಾ-ಕೊರೊನಾವೈರಸ್ ಆಗಿದೆ. ಸಾಮಾನ್ಯ ಚಿಕಿತ್ಸೆಗಳಿಗೆ ಸ್ಪಂದಿಸದ ನ್ಯುಮೋನಿಯಾದ ಅಪರಿಚಿತ ಕಾರಣಗಳನ್ನು ಹೊಂದಿರುವ ಪ್ರಕರಣಗಳ ಗುಂಪಿನ ನಂತರ, ಡಿಸೆಂಬರ್ 2019 ರಲ್ಲಿ ಚೀನಾದ ಹುಬೈ ಪ್ರಾಂತ್ಯದ ವುಹಾನ್‌ನಲ್ಲಿ ಈ ರೋಗವು ಮೊದಲು ವರದಿಯಾಗಿದೆ. ಜನವರಿ 2020 ರ ಅಂತ್ಯದ ವೇಳೆಗೆ, ಡಬ್ಲ್ಯೂ ಎಚ್ ಒ ಈ ರೋಗವನ್ನು ಸಾಂಕ್ರಾಮಿಕ ಎಂದು ಘೋಷಿಸಿತು. ಮೇ 1, 2020 ರ ಹೊತ್ತಿಗೆ, ಈ ರೋಗವು 187 ದೇಶಗಳಿಗೆ ಹರಡಿತು, ಇದು 3 ಕೋಟಿ ಜೊತೆಗೆ ಜನಸಂಖ್ಯೆಯ ಮೇಲೆ ಪರಿಣಾಮ ಬೀರಿತು.

* ಈ ಅಧ್ಯಯನವು ಆಂಜಿಯೋಟೆನ್ಸಿನ್ ಪರಿವರ್ತಿಸುವ ಕಿಣ್ವವನ್ನು (ಎಸಿಇ) ಕೋವಿಡ್ 19 ರೋಗದ ತೀವ್ರತೆಯನ್ನು ಹಿಸಲು ಸಂಭವನೀಯ ಬಯೋಮಾರ್ಕರ್ ಆಗಿ ಹಿಸಬಹುದು.

ಜೆ.ಎನ್. ಮೆಡಿಕಲ್ ಕಾಲೇಜ್, ಕೆ.ಎಲ್.ಇ.ಎಸ್. ಡಾ. ಪ್ರಭಾಕರ್ ಕೋರೆ ಚಾರಿಟೇಬಲ್ ಆಸ್ಪತ್ರೆ, ಬೆಳಗಾವಿ ಯಲ್ಲಿ ಜನವರಿ 2020 ರಿಂದ ಡಿಸೆಂಬರ್ 2020 ರವರೆಗೆ **REG NO: BG0120007** ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿ
ಮೆಡಿಸಿನ್ ಇಲಾಖೆ ನಡೆಸುತ್ತಿರುವ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನೀವು ಅರ್ಹರಾಗಿರುವುದರಿಂದ ಮೇಲಿನ ಸಂಶೋಧನೆಗೆ ನಿಮ್ಮನ್ನು ಸೇರಿಸಲು ನಿಮ್ಮನ್ನು ಕೇಳಲಾಗುತ್ತಿದೆ. ಡಾ. _____ ಅವರ ಮಾರ್ಗದರ್ಶನದಲ್ಲಿ.

ವಿಧಾನ:

ಸಂಶೋಧನಾ ಅಧ್ಯಯನದ ಭಾಗವಾಗಲು ನೀವು ಒಪ್ಪಿದರೆ, ನಿಮಗೆ ಸಂಬಂಧಿತ ಇತಿಹಾಸವನ್ನು ಕೇಳಲಾಗುತ್ತದೆ ಮತ್ತು ಸಂಬಂಧಿತ ಕ್ಲಿನಿಕಲ್ ಪರೀಕ್ಷೆ ಮತ್ತು ತನಿಖೆಗೆ ಒಳಪಡಿಸಲಾಗುತ್ತದೆ. ಅಗತ್ಯ ತನಿಖೆಗಾಗಿ ನೀವು ರಕ್ತ ಮತ್ತು ಮೂತ್ರದ ಮಾದರಿಗಳನ್ನು ಸಹ ನೀಡಬೇಕಾಗುತ್ತದೆ.

ಅಪಾಯ ಮತ್ತು ಪ್ರಯೋಜನಗಳು :

ತನಿಖೆಗಾಗಿ ನಿಮ್ಮ ತೋಳಿನಿಂದ ರಕ್ತವನ್ನು ತೆಗೆದುಕೊಳ್ಳುವಾಗ ನೀವು ಪಡೆಯುವ ಏಕೈಕ ಅಪಾಯ ಮತ್ತು ಸಂಭವನೀಯ ಅಸ್ವಸ್ಥತೆ. ರಕ್ತವನ್ನು ಎಳೆಯುವ ಸ್ಥಳದಲ್ಲಿ ಇದು ಸ್ವೀಲಿಂಗ್, ನೋವು, ಕೆಂಪು ಬಣ್ಣಕ್ಕೆ ಕಾರಣವಾಗಬಹುದು (ವಿರಳವಾಗಿ ಸಂಭವಿಸುತ್ತದೆ). ಈ ತನಿಖೆಗಳಿಂದ ನಿಮಗೆ ಪ್ರಯೋಜನವಾಗದಿರಬಹುದು ಆದರೆ ಭವಿಷ್ಯದಲ್ಲಿ ನೀವು ಇತರರಿಗೆ ಉಪಯುಕ್ತವಾಗಲಿರುವ ಈ ಅಧ್ಯಯನದ ಭಾಗವಾಗುತ್ತೀರಿ.

ಪರ್ಯಾಯಗಳು :

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವುದು ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿದೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸದಿರಲು ನೀವು ಆಯ್ಕೆ ಮಾಡಬಹುದು.

ನೀವು ಭಾಗವಹಿಸಲು ನಿರ್ಧರಿಸಿದರೆ ನೀವು ನಂತರ ನಿಮ್ಮ ಮನಸ್ಸನ್ನು ಬದಲಾಯಿಸಬಹುದು ಮತ್ತು ಅಧ್ಯಯನದಿಂದ ಹಿಂದೆ ಸರಿಯಬಹುದು. ನಿಮ್ಮ ನಿರ್ಧಾರವು ಪ್ರಸ್ತುತ ಅಥವಾ ಭವಿಷ್ಯದ ಆರೋಗ್ಯ ರಕ್ಷಣೆ ಅಥವಾ ನೀವು ಸ್ವೀಕರಿಸುವ ಇತರ ಸೇವೆಗಳನ್ನು ಬದಲಾಯಿಸುವುದಿಲ್ಲ. ಅಧ್ಯಯನ ವೈದ್ಯರು ಅಥವಾ ಪ್ರಾಯೋಜಕರು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನಿಲ್ಲಿಸಬಹುದು. ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸದಿರಲು ನೀವು ಆರಿಸಿದರೆ, ನಿಮ್ಮ ಸ್ಥಿತಿಯ ರೋಗಿಗಳಿಗೆ ನೀವು ಪ್ರಮಾಣಿತ ಚಿಕಿತ್ಸೆಯನ್ನು ಸ್ವೀಕರಿಸುತ್ತೀರಿ.

ಗೌಪ್ಯತೆ ಮತ್ತು ಗೌಪ್ಯತೆ :

ಈ ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ನಿಮ್ಮ ಬಗ್ಗೆ ಸಂಗ್ರಹಿಸಲಾದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಕಾನೂನಿನಿಂದ ಅನುಮತಿಸಲಾದ ಮಟ್ಟಿಗೆ ಗೌಪ್ಯವಾಗಿಡಲಾಗುತ್ತದೆ. ಈ ಸಂಶೋಧನಾ ದಾಖಲೆಯಲ್ಲಿ ಕೋಡ್ ಸಂಖ್ಯೆಗಳು ನಿಮ್ಮನ್ನು ಗುರುತಿಸುತ್ತವೆ. ಈ ಅಧ್ಯಯನದ ಮಾಹಿತಿಯನ್ನು ಪ್ರಕಟಿಸಬಹುದು ಆದರೆ ಯಾವುದೇ ಪ್ರಕಟಣೆಯಲ್ಲಿ ನಿಮ್ಮ ಗುರುತು ಗೌಪ್ಯವಾಗಿರುತ್ತದೆ.

ಸಂಸ್ಥೆ / ಪ್ರಾಯೋಜಕರ ನೀತಿ :

ಈ ಸಂಶೋಧನೆಗೆ ಅನ್ವಯಿಸುವುದಿಲ್ಲ

ಭಾಗವಹಿಸುವಿಕೆಗೆ ಆರ್ಥಿಕ ಪ್ರೋತ್ಸಾಹ:

ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನಿಮಗೆ ಯಾವುದೇ ಉಡುಗೊರೆಗಳನ್ನು / ಪ್ರೋತ್ಸಾಹಕಗಳನ್ನು ನೀಡಲಾಗುವುದಿಲ್ಲ / ನೀಡಲಾಗುವುದಿಲ್ಲ.

ಫಲಿತಾಂಶಗಳನ್ನು ಪ್ರಕಟಿಸಲು ಅಧಿಕಾರ :

ಅಧ್ಯಯನದ ಫಲಿತಾಂಶಗಳನ್ನು ಎಂಡಿ ಪದವಿ, ವಿಮರ್ಶೆ ಮತ್ತು ಪ್ರಕಟಣೆಯ ಪೂರ್ಣಗೊಳಿಸುವ ಅಗತ್ಯತೆಯ ಭಾಗವಾಗಿ ಬೆಲ್ಗಾಮ್‌ನ ಕೆಎಲ್‌ಇ ವಿಶ್ವವಿದ್ಯಾಲಯಕ್ಕೆ ರವಾನಿಸಲಾಗುತ್ತದೆ.

ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಅಥವಾ ಭವಿಷ್ಯದಲ್ಲಿ ನೀವು ಈ ಕೆಳಗಿನ ವ್ಯಕ್ತಿಗಳನ್ನು ಸಂಪರ್ಕಿಸಬಹುದು,

ಡಾ.ರೂಪಾ ಎಂ ಬೆಲ್ಲದ
ನೈತಿಕ ಸಮಿತಿಯ ಮುಖ್ಯಸ್ಥ
ಮಾನವ ಸಂಶೋಧನೆ,
ಜೆಎನ್ಎಂಸಿ, ಬೆಳಗಾವಿ.

ಡಾ_____
ಪ್ರೊಫೆಸರ್ ಮತ್ತು ಮುಖ್ಯಸ್ಥ
ಜನರಲ್ ಮೆಡಿಸಿನ್ ಇಲಾಖೆ,
ಜೆಎನ್ಎಂಸಿ, ಬೆಳಗಾವಿ.

REG NO: BG0120007
ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿ
ಜನರಲ್ ಮೆಡಿಸಿನ್ ಇಲಾಖೆ,
ಜೆಎನ್ಎಂಸಿ, ಬೆಳಗಾವಿ.

.

ಒಪ್ಪಿಗೆ ಪತ್ರ

" ಕೋವಿಡ್ -19 ನಲ್ಲಿ ಸೀರಮ್ ಆಂಜಿಯೋಟೆನ್ಸಿನ್ ಎಂಜೈಮ್ ಮಟ್ಟವನ್ನು ಸಂಭಾವ್ಯ ಬಯೋಮಾರ್ಕರ್ ಆಗಿ ಪರಿವರ್ತಿಸುವ ಕ್ಲಿನಿಕಲ್ ಸ್ಟಡಿ".

ಕೆಳಗೆ ಸಹಿ ಮಾಡುವ ಮೂಲಕ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನಾನು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಒಪ್ಪುತ್ತೇನೆ. ನಾನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಹಿಂತೆಗೆದುಕೊಳ್ಳಬಹುದು. ಈ ಫಾರ್ಮ್ಗೆ ಸಹಿ ಮಾಡುವ ಮೂಲಕ ನಾನು ನನ್ನ ಯಾವುದೇ ಕಾನೂನು ಹಕ್ಕುಗಳನ್ನು ಬಿಟ್ಟುಕೊಡುತ್ತಿಲ್ಲ. ಕೆಳಗಿನ ನನ್ನ ಸಹಿ ನಾನು ಈ ಒಪ್ಪಿಗೆಯ ಫಾರ್ಮ್ ಅನ್ನು ಓದಿದ್ದೇನೆ ಅಥವಾ ಈ ಸಮ್ಮತಿಯ ಫಾರ್ಮ್ ಅನ್ನು ನನಗೆ ಓದಿದ್ದೇನೆ ಮತ್ತು ಎಲ್ಲಾ ಪ್ರಶ್ನೆಗಳಿಗೆ ಉತ್ತರಿಸಿದೆ ಎಂದು ಸೂಚಿಸುತ್ತದೆ

ಭಾಗವಹಿಸುವವರ ಅಥವಾ ಕಾನೂನುಬದ್ಧವಾಗಿ ಅಧಿಕೃತ ಪ್ರತಿನಿಧಿಯ ಸಹಿ / ಎಡ ಹೆಬ್ಬೆರಳು ಮುದ್ರಣ ಭಾಗವಹಿಸುವವರ ಹೆಸರು: ....

ಸಹಿ / ಎಡ ಹೆಬ್ಬೆರಳು ಅನಿಸಿಕೆ: ....

ಭಾಗವಹಿಸುವವರ ಕಾನೂನುಬದ್ಧವಾಗಿ ಅಧಿಕಾರ ಪಡೆದವರ ಹೆಸರು: ....

ಪ್ರತಿನಿಧಿ / ರಕ್ಷಕ ಸಹಿ / ಎಡ ಹೆಬ್ಬೆರಳು ಅನಿಸಿಕೆ: ....

ಸಾಕ್ಷಿ ಹೆಸರು: ....

ಸಹಿ / ಎಡ ಹೆಬ್ಬೆರಳು ಅನಿಸಿಕೆ: ....

ತನಿಖಾಧಿಕಾರಿ ಹೆಸರು ಮತ್ತು ಸಹಿ: ....

ದಿನಾಂಕ:

ಸ್ಥಳ:

माहितीपूर्ण संमती

कोविड -19 मध्ये संभाव्य बायोमार्कर म्हणून एन्झाइम पातळी रूपांतरित करणारे सीरम एंजियोटेंसीनचे क्लिनिकल अभ्यास

प्रधान अन्वेषक: - **REG NO: BG0120007**

पदव्युत्तर विद्यार्थी,

सामान्य औषध विभाग,

जेएनएमसी, बेळगाव.

मार्गदर्शन:- डॉ._____

कुलसचिव आणि एक युनिटचे प्रमुख

सामान्य औषध विभाग,

जे.एन.एम.सी, बेळगावी.

परिचय आणि उद्देश: -

कोरोनाव्हायरस रोग-19 (कोविड-19)ची साथीची आजार बरीच गंभीर विकृती आणि मृत्यूशी संबंधित आहे. कोविड -19 चे कारक एजंट गंभीर तीव्र श्वसन सिंड्रोम कोरोनाव्हायरस -2 (सार्स-सी ओ व्ही -2) म्हणून ओळखले जाते. लिंबली गेलेली राइबोन्यूक्लिक असिड (आर एन ए) बीटा-कोरोनाव्हायरस ही कादंबरी आहे. न्यूमोनियाची अज्ञात कारणे असलेल्या क्लस्टरने नेहमीच्या उपचारांना प्रतिसाद न दिल्यास डिसेंबर 2019 मध्ये चीनच्या हुबेई प्रांतात वुहानमध्ये हा रोग प्रथम नोंदविला गेला. जानेवारी 2020 च्या अखेरीस डब्ल्यूएचओने हा आजार (साथीचा रोग) सर्व देशभर (किंवा खंडभर) असलेला म्हणून घोषित केला. 1 मे 2020 पर्यंत, हा आजार 187 देशांमध्ये पसरला होता, ज्यामुळे 3 कोटी अधिक लोकसंख्या होती. * या अभ्यासानुसार कोविड-19 रोगाच्या तीव्रतेचा अंदाज लावण्यासाठी अँजिओटेंसीन कन्व्हर्टींग एन्झाइम (एसीई) संभाव्य बायोमार्कर म्हणून भाकीत करता येईल.

जे एन मेडिकल कॉलेज,, **REG NO: BG0120007** पदव्युत्तर विद्यार्थी द्वारा आयोजित करण्यात आलेल्या 20 जानेवारी ते डिसेंबर 2020 या कालावधीत केएलईएस डॉ. प्रभाकर कोरे चॅरिटेबल हॉस्पिटल, बेलागावी येथे घेतलेल्या अभ्यासामध्ये आपण भाग घेण्यासाठी पात्र ठरल्यामुळे वरील संशोधनात स्वतःला नोंदणी करण्यास सांगितले जाईल. डॉ. _____ यांच्या मार्गदर्शनाखाली.

प्रक्रियाः

आपण संशोधन अभ्यासाचा भाग होण्यास सहमत असल्यास, आपणास संबंधित इतिहास विचारला जाईल आणि संबंधित क्लिनिकल परीक्षा आणि तपासणीस पात्र केले जाईल. आवश्यक तपासणीसाठी आपल्याला रक्त आणि लघवीचे नमुने देखील द्यावे लागतील.

जोखीम आणि फायदे :

तपासणीसाठी आपल्या बाहेरून रक्त घेत असताना आपल्याला फक्त धोका आणि संभाव्य असुविधाची समस्या उद्भवू शकते. ज्या स्थानावरून रक्त काढले आहे त्या जागेवर सूज, वेदना, लालसरपणा (क्वचितच घडते) होऊ शकतो. या तपासणीमुळे आपल्याला फायदा होणार नाही परंतु भविष्यात इतरांना उपयुक्त ठरणाया या अभ्यासाचा तुम्ही भाग व्हाल.

विकल्पः

या अभ्यासामध्ये भाग घेणे ऐच्छिक आहे. आपण या अभ्यासामध्ये भाग न घेणे निवडू शकता.

आपण भाग घेण्याचे ठरविल्यास आपण नंतर आपले मत बदलू आणि अभ्यासापासून दूर जाऊ शकता. आपल्या निर्णयामुळे आपल्याला प्राप्त झालेल्या सद्य किंवा भविष्यातील आरोग्य सेवा किंवा इतर सेवा बदलणार नाहीत. अभ्यास डॉक्टर किंवा प्रायोजक या अभ्यासात आपला सहभाग कधीही थांबवू शकतात. आपण अभ्यासामध्ये भाग न घेणे निवडल्यास, आपल्या अट असलेल्या रूग्णांसाठी तुम्हाला प्रमाणित उपचार मिळेल.

गोपनीयता आणि गोपनीयता :

या अभ्यासाच्या दरम्यान आपल्याबद्दल संकलित केलेली सर्व माहिती कायद्याद्वारे परवानगी असलेल्या मर्यादेपर्यंत गोपनीय ठेवली जाईल. कोड नंबर आपल्याला या संशोधन रेकॉर्डमध्ये ओळखतील. या अभ्यासावरील माहिती प्रकाशित केली जाऊ शकते परंतु आपली ओळख कोणत्याही प्रकाशनात गोपनीय असेल.

संस्था / प्रायोजक यांचे धोरणः

या संशोधनास लागू होत नाही

सहभागासाठी आर्थिक प्रोत्साहनः

अभ्यासामध्ये भाग घेण्यासाठी आपल्याला कोणत्याही भेटवस्तू / प्रोत्साहन दिले जाणार नाहीत.

परिणाम प्रकाशित करण्यासाठी अधिकृतताः

अभ्यासाचे निकाल एमडी पदवी, आढावा आणि प्रकाशन पूर्ण करण्याच्या आवश्यकतेनुसार केएलई विद्यापीठ, बेळगाव येथे पाठविले जातील.

अभ्यासाच्या वेळी किंवा भविष्यातील प्रश्नांच्या बाबतीत आपण खालील व्यक्तींशी संपर्क साधू शकता,

डॉ. रूपा एम बेल्लद

अध्यक्ष, नैतिक समिती मानव संशोधन

जे.एन.एम.सी, बेळगावी.

डॉ. _____

प्राध्यापक आणि प्रमुख

सामान्य औषध विभाग,

जे.एन.एम.सी, बेळगावी.

REG NO: BG0120007

पदव्युत्तर विद्यार्थी

सामान्य औषध विभाग,

जे.एन.एम.सी, बेळगावी.

संमती फॉर्म

कोविड -19 मध्ये संभाव्य बायोमार्कर म्हणून एन्झाइम पातळी रूपांतरित करणारे सीरम एंजियोटेंसीनचे क्लिनिकल अभ्यास

मी खाली स्वाक्षरी करून या अभ्यासात भाग घेण्यास स्वेच्छेने सहमत आहे. मी कधीही माघार घेऊ शकतो. या फॉर्मवर सही करून मी माझा कोणताही कायदेशीर हक्क सोडत नाही. खाली माझी स्वाक्षरी सूचित करते की मी हा संमती फॉर्म वाचला आहे किंवा हा संमती फॉर्म मला वाचला आहे आणि मला सर्व प्रश्नांची उत्तरे दिली आहेत

सहभागी किंवा कायदेशीररित्या अधिकृत प्रतिनिधीची सही / डावा अंगठा प्रिंट

सहभागीचे नाव: ....

स्वाक्षरी / डावा अंगठा ठसा: ....

सहभागीचा

कायदेशीररीत्या अधिकृत नाव: ....

प्रतिनिधी / पालक

स्वाक्षरी / डावा अंगठा ठसा: ....

साक्षीचे नाव: ....

स्वाक्षरी / डावा अंगठा ठसा: ....

अन्वेषकांचे नाव आणि स्वाक्षरीः ....

तारीख:

ठिकाणः

PROFORMA

Patient name:

Age/Sex: DOA:

Religion:

Address:

Phone number: Occupation:

CHIEF COMPLAINTS:

PRESENT HISTORY

PAST HISTORY:

FAMILY HISTORY

PERSONAL HISTORY

TREATMENT HISTORY

EXAMINATION: GENERAL CONDITION: PALLOR- YES/NO

ICTERUS-YES/NO

LYMPHADENOPATHY-YES/NO CYANOSIS- YES/NO

CLUBBING-YES/NO

EDEMA-YES/NO O/E:

Temperature: Pulse rate: Resp Rate Blood pressure:

S/E:

CVS

RS

PA

CNS

INVESTIGATIONS:	DATE:	INFERENCE:
Hemoglobin		
Total leucocyte count		
Differential leucocyte count Platelet count Serum ACE levels Hs-reactive protein		
Interleukin-6		
Erythrocyte sedimentationrate (ESR)		
D dimer		
Total bilirubin		
Direct bilirubin Indirect bilirubin		
SGOT		
SGPT		
Alkaline phosphatase		
Serum albumin		
Serum globulin		
Urea		
Creatinine		
Blood group		
IMAGING HRCT THORAX (CT severity score)		

TREATMENT:

CONCLUSION:

AGE	IP NO	SEX	DOA	CHIEF COMPLAINTS	COMORBIDITIES	PULSE RATE	BLOOD PRESSURE	SPO2 (ADMISSION O2 SATURATION)	HRCT THORAX (CT SEVERITY SCORE)	RT PCR POSITIVE	HEMOGLOBIN	TOTAL LEUCOCYTE COUNT	PLATELET COUNT	ESR	D dimer	INTERLEUKIN 6	Hs-REACTIVE PROTEIN	SERUM ACE LEVELS	TOTAL BILIRUBIN	DIRECT BILIRUBIN	SGOT	SGPT	ALKALINE PHOSPHATASE	SERUM ALBUMIN	UREA	CREATININE	OUTCOME
42	6089222	M	17.05.21	Breathlessness and Headache	T2DM	90	110/70	78% on O2 mask	CORADS 5 12/25	Positive	14.5	14.7	2,30,000	6	550	12.34	53.4	<5	0.58	0.26	22	49	84	2.8	27	6.6	Improved
56	1052640	F	17.05.21	Breathlessness, cough, fever	T2DM	78	130/90	90% on O2 mask	CORADS 5 12/25	Positive	12.4	10	1,56,000	10	300	4.5	7.3	21	0.11	0.12	25	20	120	3.8	19	0.58	Improved
55	1051978	M	22.05.21	Breathlessness	No comorbidities	104	110/70	94% on O2 mask	CORADS 5 14/25	Positive	14.1	9.7	20,600	32	482	15	187.5	15	0.58	0.52	23	37	100	3.8	20	0.2	Improved
77	1053391	M	12.05.21	Breathlessness	Hypertension	78	130/80	87% on O2 mask	CORADS 5 4/25	Positive	14.6	18.5	4,52,000	66	553	79	90	<5	1.64	0.54	339	587	211	3.2	47	0.69	Improved
47	1051960	M	09.05.21	Cough, Breathlessness	No comorbidities	90	120/80	80% on O2 mask	CORADS 5 10/25	Positive	15.8	3.1	1,00,000	28	448	65.06	90.9	69	0.38	0.68	47	25	57	3.8	24	1.06	Improved
69	1028755	M	21.11.20	Breathlessness	T2DM and Hypertension	121	110/70	92% on O2 mask	CORADS 5 20/25	Positive	10.3	20.4	2,74,000	44	506.7	452.3	170.1	63	0.58	0.39	18	13	180	2.5	168	5.4	Improved
73	1052756	M	19.05.21	Cough, Fever	No comorbidities	86	160/90	93% on O2 mask	CORADS 5 4/5	Positive	13	12.6	2,24,000	21	302	100	115	10	0.80	0.25	27	26	52	3.7	25	0.76	Improved
48	1049655	M	18.04.21	Fever and headache	No comorbidities	136	130/80	97%	CORADS 5 10/25	Positive	14.9	12	2,37,000	18	593	4.98	265.8	19	0.90	0.50	73	37	133	3.2	36	0.8	Improved
64	1048047	M	05.04.21	Fever and Cough	No comorbidities	88	110/80	92% on O2 mask	CORADS 5 10/25	Positive	13.6	11.4	2,28,000	7	292	629.41	50.3	<5	0.36	0.17	0.19	21	19	3.1	96	0.7	Improved
44	1052405	F	14.05.21	Fever and Cough	No comorbidities	98	110/70	99%	CORADS 5 18/25	Positive	10.8	2400	1,53,000	37	548	212.3	88.1	11	0.20	0.10	190	76	70	3.5	25	0.92	Improved
82	1052719	M	18.05.21	Breathless and Cough	No comorbidities	108	130/90	27% intubated	CORADS 5 12/25	Positive	9.2	11	2,18,000	6	793	78.31	157.5	20	0.50	0.10	61	16	100	3.3	104	3.4	Expired
19	1052769	F	19.05.21	Cough, Fever and Breathlessness	No comorbidities	130	105/72	90% on O2 mask	CORADS 5 12/25	Positive	11.5	13	3,22,000	20	723	42.6	66	28	0.40	0.12	31	18	116	2.8	10	0.5	Improved
29	1056833	M	15.05.21	Breathless and Cough	No comorbidities	108	110/70	84% on O2 mask	CORADS 5 13/25	Positive	13.2	11.1	2,39,000	42	442	22.41	15.4	6	0.13	0.13	39	26	71	3.6	39	0.57	Improved
73	1052839	M	19.05.21	Giddiness	No comorbidities	90	130/90	70% on NIV	CORADS 5 9/25	Positive	12.5	5.3	1,65,000	40	1065	61.9	45.9	8	0.83	0.46	30	16	54	3.7	35	1.41	Improved
65	1052530	F	13.05.21	Breathlessness and Fever	No comorbidities	82	90/60	62% intubated	CORADS 5 8/25	Positive	12.8	22.6	1,17,000	15	5000	48.71	269	13	2.11	2.00	60	29	280	4	94	0.91	Improved
38	1052786	F	19.05.21	Body ache and Fever	T2DM	96	120/80	90% on O2 mask	CORADS 5 14/25	Positive	11	8.6	1,98,000	6	554	82.62	70	32	0.80	0.20	20	36	116	4.2	70	0.9	Improved
58	1052557	F	16.05.21	Breathlessness and weakness	T2DM, HTN, hypothyroidism	117	130/80	94% on O2 mask	CORADS 5 11/25	Positive	10	9	2,63,000	49	351	52.24	16.1	46	0.26	0.14	16	12	70	4.4	34	0.63	Improved
32	1049614	M	18.04.21	Fever, Hemoptysis and Breathlessness	No comorbidities	88	120/80	95% on O2 mask	CORADS 5 10/25	Positive	15.6	8.7	33,000	39	1139	46	110	9	1.28	0.56	140	153	73	3.6	34	0.85	Improved
67	1052510	M	16.05.21	Fever, Cough and Breathlessness	Hypertension	120	140/70	98%	CORADS 5 10/25	Positive	12.2	9	2,44,000	49	>5000	1714	222	19	0.85	0.86	173	139	453	3.1	121	1.41	Expired
66	1052537	F	16.05.21	Fever	No comorbidities	86	140/70	92% on O2 mask	CORADS 5 12/25	Positive	11.1	6.7	1,57,000	91	661	116	143.5	17	0.25	0.16	20	12	84	3.6	45	0.81	Improved
55	1052484	F	15.05.21	Generalised weakness, cough and fever	No comorbidities	130	130/80	98%	CORADS 5 10/25	Positive	13	7.7	1,96,000	24	552	17.26	197.1	18	0.24	0.09	26	25	104	3.2	59	0.88	Improved
63	1052621	F	17.05.21	Cough	No comorbidities	90	100/70	84% on O2 mask	CORADS 5 16/25	Positive	10.2	7.4	2,81,000	62	305	34.5	138	14	0.33	0.22	29	15	70	3.7	18	0.75	Improved
78	1035337	M	17.01.21	Breathlessness	No comorbidities	68	124/68	95%	CORADS 5 17/25	Positive	13	8.7	1,97,000	65	490	79.48	209.4	9	1.90	1.20	77	58	52	3.3	38	0.92	Improved
63	6089201	M	17.05.21	Chest and Shoulder pain	No comorbidities	67	148/106	97%	CORADS 5 11/25	Positive	12.6	15.9	2,99,000	16	159	32.02	34.2	<5	0.33	0.20	20	15	96	3.8	15	0.66	Improved
68	1034502	M	31.01.21	Fever	No comorbidities	88	126/80	72% on NIV	CORADS 5 16/25	Positive	14.5	12.3	2,33,000	56	529	16	79.6	24	0.33	0.10	31	32	190	3.5	13	0.78	Improved
58	1052557	F	16.05.21	Breathlessness, weakness and Cough	Hypothyroidism	120	130/80	95%	CORADS 5 13/25	Positive	10	9	2,63,000	49	351	52.24	16.1	43	0.26	0.14	16	12	70	4.4	34	0.63	Improved
59	1052044	M	10.05.21	Breathlessness, fever, cough and myalgia	Hypertension and lymphoma	88	120/80	88% on O2 mask	CORADS 5 22/25	Positive	8.4	11.6	22,000	14	800	13.5	258	14	0.15	0.10	28	17	180	4	30	0.75	Improved
40	1052466	F	15.05.21	Breathlessness, cough and fever	No comorbidities	108	126/80	95%	CORADS 5 14/25	Positive	14.2	18.7	3,26,000	12	5000	12.18	43.8	10	0.32	0.06	33	38	53	3.8	20	0.5	Improved
55	1052362	F	13.05.21	Breathlessness	No comorbidities	88	100/70	93% on O2 mask	CORADS 5 19/25	Positive	10.5	11.8	2,94,000	9	585	5.79	40	16	0.20	0.10	42	44	78	4.1	24	1.3	Improved
54	1049362	M	16.04.21	Fever	T2DM	86	100/70	80% on O2 mask	CORADS 5 12/25	Positive	11.6	5.4	1,70,000	77	783	24	119.6	16	0.32	0.20	26	14	91	3	57	1.44	Improved
54	1052404	M	14.05.21	Breathlessness	No comorbidities	84	108/70	94%	CORADS 5 19/25	Positive	16.6	15.1	2,14,000	25	1370	53.3	17.6	18	0.75	0.13	21	25	139	3.6	59	0.7	Improved
30	1051805	M	07.05.21	Breathlessness and Fever	No comorbidities	78	120/80	95%	CORADS 5 14/25	Positive	12.7	9.7	2,07,000	47	372	209	1.5	20	0.29	0.20	44	29	180	3.8	18	1	Improved
51	1051993	F	09.05.21	Fever	No comorbidities	78	130/90	96%	CORADS 5 10/25	Positive	12.2	3.9	1,50,000	34	612	5.23	58.2	<5	0.40	0.20	33	25	72	3.9	23	0.59	Improved
35	1049868	M	20.04.21	Breathlessness and Fever	T2DM	113	130/80	92% on O2 mask	CORADS 5 14/25	Positive	13.5	15.8	2,72,000	70	736	74.17	83.2	11	0.53	0.22	17	49	68	3.0	40	0.7	Expired
42	1052335	M	03.05.21	Fever and Cough	No comorbidities	102	114/70	90% on O2 mask	CORADS 5 10/25	Positive	13.4	6.4	2,92,000	21	387	1.5	6.7	8	0.36	0.15	209	194	86	4.0	22	0.83	Improved
57	1052120	F	11.05.21	Fever	No comorbidities	97	120/80	95%	CORADS 5 16/25	Positive	11.5	4.6	1,28,000	27	6743	59.96	119.7	14	0.87	0.47	51	21	99	2.9	33	0.47	Expired
73	1052511	M	16.05.21	Breathlessness	No comorbidities	84	88/50	97%	CORADS 5 17/25	Positive	13.2	8.1	1,95,000	49	537	351.1	195.1	14	0.52	0.34	113	62	94	3.6	43	0.97	Expired

AGE	IP NO	SEX	DOA	CHIEF COMPLAINTS	COMORBIDITIES	PULSE RATE	BLOOD PRESSURE	SPO2 (ADMISSION O2 SATURATION)	HRCT THORAX (CT SEVERITY SCORE)	RT PCR POSITIVE	HEMOGLOBIN	TOTAL LEUCOCYTE COUNT	PLATELET COUNT	ESR	D dimer	INTERLEUKIN 6	Hs-REACTIVE PROTEIN	SERUM ACE LEVELS	TOTAL BILIRUBIN	DIRECT BILIRUBIN	SGOT	SGPT	ALKALINE PHOSPHATASE	SERUM ALBUMIN	UREA	CREATININE	OUTCOME
73	1027390	M	07.11.20	Cough	T2DM and Hypertension	78	110/70	90% on O2 mask	CORADS 5 4/25	Positive	9.5	13.7	2,05,000	6	968	121.6	292	22	0.42	0.30	48	16	38	2.6	102	3.72	Expired
33	1049611	M	18.04.21	Fever	No comorbidities	96	130/80	94%	CORADS 5 6/25	Positive	15.2	7.7	2,06,000	32	208	68	14.5	22	0.77	0.27	19	26	56	4.0	34	0.73	Improved
37	1049618	M	18.04.21	Breathlessness and Cough	T2DM	72	130/80	92% on O2 mask	CORADS 5 13/25	Positive	15.1	5.7	1,95,000	16	417	77.95	16.4	17	0.49	0.33	70	56	123	3.9	26	0.64	Improved
46	1049363	M	16.04.22	Cough	No comorbidities	96	100/60	75% on NIV	CORADS 5 6/25	Positive	11.7	3.9	1,21,000	19	218	98	55.9	11	0.49	0.20	186	113	46	3.6	14	1	Improved
65	1050512	F	17.04.21	Breathlessness and cough	No comorbidities	104	130/70	86% on O2 mask	CORADS 5 13/25	Positive	11.8	9.5	2,39,000	76	4066	10.19	183.2	36	0.45	0.18	141	59	130	3.8	39	0.98	Expired
63	1029556	M	20.11.20	Breathlessness	T2DM and Hypertension	66	130/80	99%	CORADS 5 13/25	Positive	9.9	9	2,47,000	79	1329	144.3	90	31	0.23	0.13	24	10	80	209	183	10.89	Expired
60	1036428	M	24.01.21	Weakness	No comorbidities	110	120/70	100%	CORADS 5 12/25	Positive	14.4	12.1	3,37,000	26	1460	246.4	176.1	<5	0.39	0.28	52	26	87	3.3	52	1.19	Expired
55	1048958	M	12.04.21	Fever and Cough	No comorbidities	88	110/80	94%	CORADS 5 10/25	Positive	10.7	5.6	1,77,000	31	306	30.88	96.1	23	0.23	0.17	36	25	69	3.5	63	1.7	Improved
52	1049596	M	17.04.21	Fever, Cough and Breathlessness	No comorbidities	86	100/70	60% intubated	CORADS 5 6/25	Positive	16.1	17.2	2,11,000	20	363	116.9	186.8	14	0.68	0.40	23	33	95	3.4	53	0.84	Improved
44	1048743	M	10.04.21	Fever	No comorbidities	100	120/80	93% on O2 mask	CORADS 5 6/25	Positive	14.4	4.4	1,50,000	53	1800	19.17	130	<5	0.42	0.22	50	53	67	4.0	19	1.2	Improved
34	1049355	M	16.04.21	Cough	No comorbidities	90	110/80	93% on O2 mask	CORADS 5 15/25	Positive	13.5	7.1	2,10,000	20	680	16	82.3	<5	0.61	0.22	18	22	54	4.3	21	1.20	Improved
70	1028572	M	20.11.20	Breathlessness	T2DM and Hypertension	100	140/80	98%	CORADS 5 10/25	Positive	9.2	17.9	4,79,000	36	957	1.5	14.9	20	0.28	0.09	26	16	100	3.8	60	1.91	Improved
61	1052858	F	20.05.21	Generalised weakness, cough and fever	T2DM and Hypertension	112	130/90	97%	CORADS 5 12/25	Positive	12	5.6	3,52,000	56	157	25.24	46.1	16	0.50	0.11	28	45	69	3.4	50	0.88	Improved
41	1049581	M	17.04.21	Cough	No comorbidities	88	130/80	95%	CORADS 5 6/25	Positive	13.5	5	1,34,000	38	217	24.97	13	16	0.24	0.14	31	23	51	4.3	17	0.91	Improved
28	1048420	M	07.04.21	Cough, Fever	Hypothyroidism	80	110/80	95%	CORADS 5 6/25	Positive	11.1	5.9	1,79,000	29	159	20.32	13.3	20	0.19	0.06	12	9	78	3.6	14	0.46	Improved
39	1049018	M	13.04.21	Breathlessness and Fever	No comorbidities	108	180/90	84% on O2 mask	CORADS 5 14/25	Positive	15	17.2	1,75,000	15	522	145	192.6	9	0.34	0.15	61	50	78	3.9	31	1.08	Expired
51	1049472	M	16.04.21	Breathlessness	No comorbidities	68	110/60	78% on O2 mask	CORADS 5 19/25	Positive	13.9	12	1,71,000	63	>5000	480	89.1	10	0.19	0.13	62	31	94	3.4	76	0.75	Improved
40	1049200	M	15.04.21	Fever, Cough and Breathlessness	No comorbidities	110	130/80	97%	CORADS 5 19/25	Positive	13.9	5.6	1,50,000	44	324	600.9	142.6	18	0.74	0.56	29	22	84	3.9	25	1.02	Improved
55	1052689	F	18.05.21	Breathlessness and weakness	Hypertension	100	120/70	92% on O2 mask	CORADS 5 4/25	Positive	11.3	6.5	2,26,000	17	1312	142.3	66.2	24	0.35	0.10	44	42	61	3.9	28	0.68	Expired
59	1052144	F	12.05.21	Breathlessness and Headache	No comorbidities	126	112/70	24% intubated	CORADS 5 24/25	Positive	11	13.4	3,34,000	87	10,524	1.50	184.6	8	0.36	0.11	44	42	73	3.2	40	0.68	Expired
55	1051814	M	07.05.21	Breathlessness	No comorbidities	130	110/70	86% on O2 mask	CORADS 5 11/25	Positive	12.8	7.4	2,18,000	55	1654	9.36	194.6	6	0.51	0.17	62	28	57	3.2	26	0.85	Improved
19	1049631	F	17.04.21	Cough, Fever and Generalised weakness	No comorbidities	88	100/60	70% on NIV	CORADS 5 14/25	Positive	13.3	5600	1,65,000	14	168	6.46	84	16	0.19	0.09	18	13	92	4.6	13	0.7	Improved
54	1049643	M	24.04.21	Headache	No comorbidities	100	110/70	87% on O2 mask	CORADS 5 18/25	Positive	14.1	15	90,0000	27	235	5.18	18.2	22	0.54	0.14	17	38	95	3.0	42	0.63	Improved
38	1036881	M	28.01.21	Generalised weakness	No comorbidities	68	170/80	90% on O2 mask	CORADS 5 18/25	Positive	10.6	13	64,000	71	>5000	480	69	7	0.78	0.30	25	33	73	3.8	26	1.08	Improved
63	1051643	M	06.05.21	Fever	No comorbidities	90	110/70	86% on O2 mask	CORADS 5 18/25	Positive	12.6	9.2	1,95,000	54	612	37	187.4	9	0.20	0.06	56	40	110	4.5	114	3.46	Improved
55	1051809	M	04.05.21	Cough	No comorbidities	78	120/70	80% on O2 mask	CORADS 5 24/25	Positive	15.6	12.6	4,26,000	47	1403	55.4	59.9	16	1.30	1.0	44	39	198	3.9	48	0.88	Improved
55	1049857	M	07.05.21	Fever	No comorbidities	88	130/80	88% on O2 mask	CORADS 5 15/25	Positive	11.8	10.9	1,21,000	59	1326	104.6	225	13	0.6	0.5	17	34	192	3.6	39	0.6	Improved
65	1051393	M	03.05.21	Fever	No comorbidities	88	140/90	92% on O2 mask	CORADS 5 5/25	Positive	13.4	5.6	1,93,000	25	5000	20	113.6	18	0.44	0.44	31	19	110	3.6	39	0.81	Improved
45	1051271	M	02.05.21	Fever	T2DM	88	160/90	54% intubated	CORADS 5 18/25	Positive	14.1	5.7	1,85,000	31	500	19.43	149.9	18	0.48	0.40	57	30	100	3.6	45	0.71	Improved
35	1051255	M	02.05.21	Fever	No comorbidities	88	140/60	62% on NIV	CORADS 5 13/25	Positive	8.7	21.5	1,43,000	56	5000	86	135.7	20	0.49	0.40	32	65	118	4.0	64	0.89	Expired
51	1051731	F	06.05.21	Fever	No comorbidities	80	100/60	78% on NIV	CORADS 5 9/25	Positive	14.4	17.3	2,30,000	9	377	22	110	13	0.67	0.50	65	48	117	4.5	47	0.68	Improved
38	1051823	F	08.05.21	Fever	No comorbidities	80	120/70	75% on NIV	CORADS 5 17/25	Positive	14.2	8.6	2,17,000	52	1431	183	131	16	0.40	0.28	59	40	100	4.0	27	0.68	Improved
65	1050836	F	22.04.21	Fever	No comorbidities	88	110/80	95%	CORADS 5 16/25	Positive	8.6	4.1	62,000	17	573	20.11	176	43	0.73	0.23	10	31	100	4.2	20	0.82	Improved
54	1051836	F	08.05.21	Fever	No comorbidities	96	200/100	57% intubated	CORADS 5 16/25	Positive	12.1	21.6	2,90,000	12	1378	20	102	19	0.35	0.10	40	15	106	3.8	73	1.01	Improved
75	1051477	M	04.05.21	Breathlessness	Hypertension	90	110/70	88% on O2 mask	CORADS 5 17/25	Positive	12.2	3.8	1,13,000	62	1026	23	226	26	0.41	0.40	73	22	108	4.2	81	1.31	Improved
44	1051522	F	05.05.21	Fever	No comorbidities	88	130/90	67% on NIV	CORADS 5 22/25	Positive	14	13.1	1,60,000	8	943	45	274	16	0.62	0.12	41	55	110	4.0	11.5	0.75	Expired
38	1050847	M	07.05.21	Breathlessness	No comorbidities	24	120/70	73% on NIV	CORADS 5 21/25	Positive	13.4	14	2,32,000	36	1530	300	109	15	0.37	0.37	22	27	118	4.0	42	0.72	Improved

AGE	IP NO	SEX	DOA	CHIEF COMPLAINTS	COMORBIDITIES	PULSE RATE	BLOOD PRESSURE	SPO2 (ADMISSION O2 SATURATION)	HRCT THORAX (CT SEVERITY SCORE)	RT PCR POSITIVE	HEMOGLOBIN	TOTAL LEUCOCYTE COUNT	PLATELET COUNT	ESR	D dimer	INTERLEUKIN 6	Hs-REACTIVE PROTEIN	SERUM ACE LEVELS	TOTAL BILIRUBIN	DIRECT BILIRUBIN	SGOT	SGPT	ALKALINE PHOSPHATASE	SERUM ALBUMIN	UREA	CREATININE	OUTCOME
43	1051644	M	06.05.21	Fever	No comorbidities	90	80/50	93% on O2 mask	CORADS 5 14/25	Positive	14.5	12.7	2,67,000	58	1417	22	36.4	18	0.32	0.20	759	600	100	4.62	62	0.15	Improved
60	1051262	M	02.05.21	Cough	No comorbidities	90	120/70	96%	CORADS 5 10/25	Positive	13.6	4.1	1,61,000	70	327	96	78.8	14	0.31	0.30	51	33	112	4.5	35	0.87	Improved
62	1051304	M	03.05.21	Breathlessness	No comorbidities	80	140/80	89% on O2 mask	CORADS 5 17/25	Positive	15	6.3	1,60,000	10	466	40.5	58	13	0.86	0.50	77	44	117	4.0	83	0.73	Improved
42	1051193	M	01.05.21	Fever	No comorbidities	80	130/70	90% on O2 mask	CORADS 5 11/25	Positive	13.2	8.9	2,25,000	26	247	64	195.7	13	0.55	0.25	29	16	160	4.0	38	1.3	Improved
38	1050453	M	23.05.21	Fever	No comorbidities	88	110/80	76% on NIV	CORADS 5 13/25	Positive	13.5	10.1	1,98,000	23	5000	57.34	297	14	0.77	0.55	47	65	180	4.0	60	0.84	Improved
51	1051196	M	01.05.21	Breathlessness	No comorbidities	88	90/60	63% on NIV	CORADS 5 6/25	Positive	8.5	15.6	3,34,000	21	395	223.8	155.4	14	1.68	1.00	21	14	107	3.8	44	1.01	Improved
37	1051210	F	01.05.21	Fever	No comorbidities	88	130/80	93% on O2 mask	CORADS 5 4/25	Positive	14.1	12.1	1,24,000	42	518	221	57.5	13	1.25	0.25	17	17	104	2.5	29	0.75	Improved
52	1051213	M	07.05.21	Fever and Breathlessness	No comorbidities	76	100/80	88% on O2 mask	CORADS 5 18/25	Positive	14.7	7.2	89,000	7	609	3.65	107	17	1.10	0.80	55	44	108	3.9	28	0.73	Improved
38	1050847	M	22.04.21	Fever	No comorbidities	82	120/70	73% on NIV	CORADS 5 21/25	Positive	13.4	14	2,32,000	9	1530	10	109	12	0.37	0.10	22	27	180	3.4	42	0.72	Improved
65	1051907	F	08.05.21	Fever	No comorbidities	70	110/70	70% on NIV	CORADS 5 23/25	Positive	9.2	10.3	2,83,000	10	831	9	307.1	14	0.3	0.14	23	13	100	4.2	62	1.6	Improved
77	1051910	M	08.05.22	Fever	No comorbidities	88	110/70	94% on O2 mask	CORADS 5 10/25	Positive	13.8	9.1	1,50,000	15	>5000	16	146.8	14	1.33	0.80	35	27	122	3.9	41	1.64	Improved
56	1051613	M	05.05.21	Breathlessness	No comorbidities	70	110/80	92% on O2 mask	CORADS 5 15/25	Positive	13.2	10.5	2,70,000	41	598	40	89.8	18	1.14	1.10	57	98	172	4.0	39	0.8	Improved
37	1051596	M	05.05.21	Fever	No comorbidities	80	120/70	90% on O2 mask	CORADS 5 7/25	Positive	12.9	3.5	2,00,000	21	217	10	14.2	19	0.77	0.50	69	54	100	3.9	23	0.75	Improved
46	1051610	F	05.05.21	Fever	No comorbidities	88	130/90	80% on O2 mask	CORADS 5 6/25	Positive	15.8	15	2,40,000	47	1416	46	150	17	0.48	0.22	22	24	100	3.5	57	0.81	Improved
29	1050024	M	20.04.21	Fever	No comorbidities	90	120/80	68% on NIV	CORADS 5 17/25	Positive	13.9	11.4	1,94,000	51	4292	94	114	48	0.27	0.20	65	68	100	4.5	32	1.0	Improved
75	1021495	M	22.08.21	Cough	No comorbidities	90	120/70	88% on O2 mask	CORADS 5 13/25	Positive	11.7	6.6	2,27,000	9	181	1.56	4.8	20	0.42	0.40	24	22	110	4.1	25	0.62	Improved
65	1019426	M	23.06.21	Fever and Cough	No comorbidities	88	130/90	92% on O2 mask	CORADS 5 6/25	Positive	14.1	7.2	1,61,000	50	746	32	111.5	20	0.50	0.40	54	42	130	4.0	31	0.79	Improved
56	1051866	F	08.05.21	Fever	No comorbidities	88	110/90	85% on O2 mask	CORADS 5 12/25	Positive	11.6	17.9	2,01,000	33	308	42	140	55	0.33	0.13	58	61	190	4.2	46	0.8	Improved
34	1051807	M	07.05.21	Fever	No comorbidities	88	110/70	95%	CORADS 5 16/25	Positive	13.9	6.4	1,98,000	10	248	6	84.3	12	0.30	0.10	41	47	90	3.9	22	0.82	Improved
51	1051918	F	09.05.21	Fever	No comorbidities	88	110/80	89% on O2 mask	CORADS 5 13/25	Positive	11.9	6.5	2,78,000	16	384	8	49.8	16	0.45	0.15	25	38	110	3.9	24	0.65	Improved
57	1051827	M	08.05.21	Fever	No comorbidities	80	110/70	88% on O2 mask	CORADS 5 21/25	Positive	11.1	12.9	3,98,000	21	1503	700	5.7	16	1.06	1.00	767	630	100	3.4	47	0.65	Improved
30	1051963	M	09.05.21	Fever	No comorbidities	88	120/80	60% intubated	CORADS 5 22/25	Positive	15.6	10.6	2,74,000	22	1252	36	15.1	33	0.75	0.25	35	44	100	3.9	58	0.91	Improved
36	1051952	M	09.05.21	Breathlessness	No comorbidities	88	110/70	91% on O2 mask	CORADS 5 24/25	Positive	11.5	14.2	2,87,000	62	437	84.9	76.6	40	0.21	0.20	33	22	100	3.9	41	0.93	Improved
88	1051902	F	08.05.21	Breathlessness	No comorbidities	108	150/80	51% intubated	CORADS 5 13/25	Positive	9.5	6.5	1,52,000	70	1344	626	36.6	26	0.39	0.10	103	13	90	3.5	41	1.32	Expired
71	1051280	F	05.05.21	Fever	No comorbidities	80	110/60	90% on O2 mask	CORADS 5 9/25	Positive	12.4	14.6	2,02,000	57	84	24	31.3	13	0.30	0.10	52	17	84.0	4.0	57	0.81	Improved
45	1051068	M	30.04.21	Generalised weakness	No comorbidities	80	124/80	97%	CORADS 5 10/25	Positive	13.6	5.1	1,50,000	62	491	62.91	66	24	0.28	0.16	58	39	130	3.9	31	0.69	Improved
45	1051693	F	06.05.21	Fever	No comorbidities	88	100/80	84% on O2 mask	CORADS 5 23/25	Positive	12.6	15.4	1,83,000	9	7155	320	79.2	13	0.27	0.20	41	18	82	4.5	41	0.85	Improved