INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor : 5.725

www.ijprems.com
editor@ijprems.com

Vol. 03, Issue 09, September 2023, pp : 379-392

HYPERFERRITINEMIA IN COVID-19

Farheen Shahid[1]

[1]BDNS, 5th Year, Department of Dietetics and Nutritional Sciences, The University Of Lahore, Islamabad Campus, Pakistan.

ABSTRACT

BACKGROUND: COVID-19 appeared first in December 2019 in Wuhan, China. Corona virus often cause severe pneumonia and also targeted different organs. The severity and mortality of COVID-19 is usually associated with inflammatory cytokine storm. Ferritin is generally a biomarker of iron deficiency but elevated serum ferritin level also exhibits inflammatory diseases. Patients with severe COVID-19 have high serum ferritin level than people with less severe COVID that is why it is related that Hyperferritinemia is more probably present in severe COVID-19.Here we focus on the role of serum ferritin for diagnostic and clinical management of patients withCOVID-19.

OBJECTIVE: To determine the association between serum ferritin levels and Covid-19. And to determine correlation of ferritin with severity of Covid-19.

METHOD: The cross-sectional study involving 152 patients was conducted at the out-patient department of Benazir Bhutto Hospital Rawalpindi. SPSS 17 was used for statistical analyses.

RESULTS: According to my study out of 152 patients, 102 were male and 50 female. 62 patients showed comorbidity with other diseases while 90 patients showed no comorbidity. 80 patients died of disease while 72 patients survived. A minimum age of patient was 17 years and maximum age was about 87 years. The minimum value of Ferritin was 15.00 and maximum value of ferritin was1000.0.

CONCLUSION: Covid-19 studies showed that serum ferritin was raised in severely infected patients that is why serum ferritin acts as biomarker of COVID-19 severity in hospitalized patients. Serum ferritin may be considered both the stratifying and prognostic biomarker of COVID-19.

Keywords: Covid -19 patients, Inflammatory cytokine storm, Serum Ferritin level, Hyperferritinemia, Inflammatiory diseases.

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19), which broke out in Wuhan, China, in December 2019 and spread around the entire world. On the 11th March 2020, the World Health Organization (WHO) declared the disease a pandemic. COVID-19 infection is characterized by complications of the lower respiratory system, including pneumonia, and clinical presentations of the disease range from asymptomatic, mild, moderate, to severe forms.[1]Immunodeficiency, senility, and other disease conditions such as diabetes, coronary heart disease, hypertension, cerebral infarction, pneumonia, severe asthma, and chronic bronchitis complicate the COVID-19 illness. SARS-CoV-2 is a single stranded RNA virus that is classified into the beta coronavirus genus and the Corona family.[1]The genome of the coronavirus encodes four predominant proteins, which are the Envelope (E), Membrane (M), Nucleocapsid (N), and Spike (S) proteins. The S protein is responsible for viral access into respiratory tissue through the Angiotensin-Converting Enzyme 2 (ACE-2) expressing epithelial cells. Being the first central point of contact with the host cell, the S protein is known to have strong immunogenic properties. There are three main clinical stages of COVID-19. Stage one is the viral response phase, which [2]is the period of early infection. It lasts for about four days, and it is typically characterized by non-specific symptoms such as fever, cough, and diarrhea. Stage two is the pulmonary phase which usually lasts between days 5 to 13. At this phase, the pulmonary symptoms are first without hypoxia, and later hypoxia develops. Stage three is the systemic hyper-inflammation phase, which is usually from day14.Most times, patients report to the hospital at end of stage 1 or the beginning of stage 2. At this time, the innate immune system's potential to combat the infection has been threatened. Evidence proposes that deaths associated with COVID-19 are principally owing to hyperinflammation and uncontrolled immune response The COVID-19 infection triggers a cytokine storm characterized by potentially life-threatening pathologies such as hyper- inflammation, septic shock complications, coagulation dysfunction, and impairment of several vital organs. Hypercytokinemia in COVID-19 patients is characterized by the speedy propagation and hyperactivation of T-cells, macrophages, natural killer (NK) cells, andthe excessive production of a host of pro-inflammatory cytokines and chemical mediators discharged by immune or non-immune cells. The early prediction, rigorous prevention, and therapeutic intervention of a cytokine release syndrome are crucial in reducing the level of morbidity and fatality related to COVID-19 [3]. The development of hypercytokinemia is a strong indication of disease progression, and immune suppression is a key therapeutic strategy

in combating this complication. Therefore, during the investigation and therapy of pneumonia caused by COVID-19 infection, it has become necessary to monitor cytokine levels and other markers to improve the rate of cure and, in turn, reduce the rate of human mortality from the burden of disease. Concerning the COVID-19 infection and the host cell, this research paper focuses on the changing pathophysiological aspects of the COVID- 19 infection, accentuating the cytokine storm's pathogenesis and markers. It also critically explores the current and potential therapeutic options that can be exploited to alleviate and control cytokine storms. Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects[4],contributing to the cytokine storm It has been reported that fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome. Many individuals with diabetes exhibit elevated serum ferritin levels, and it is known that they face a higher probability to experience serious complications from COVID-19 On this basis, we briefly review evidence supporting the hypothesis that ferritin levels might be a crucial factor influencing the severity of COVID-19.In one study with 20 COVID-19 patients, it was found that individuals with severe and very severe COVID-19 exhibited increased serum ferritin level, being serum ferritin in the very severe COVID-19 group significantly higher than in the severe COVID-19 group in agreement with this, another study revealed that in patients who died by COVID-19, ferritin levels were high upon hospital admission and throughout the hospital stay. The median values of serum ferritin levels after day of hospitalization exceeded the upper limit of detection in these patients, suggesting that ferritin levels increased non-stop Elevated ferritin levels were found also in autopsies of patients whose cause of death wasSARS-CoV-2infection.

An analysis of the peripheral blood of patients with severe COVID-19 revealed elevated levels of ferritin compared with patients with non-severe disease.[5]Therefore, it was concluded that serum ferritin levels were closely related to the severity of COVID-19. Finally, laboratory findings in patients with severe COVID-19 showed data consistent with cytokine storm involving elevated inflammatory markers, including ferritin, which has been associated with critical and life- threatening illness. A possible strategy to decrease ferritin levels might be the treatment with iron chelators. Deferoxamine may be a good candidate, since is a non-toxic iron chelator clinically approved by the FDA and is effective for long-term iron chelation therapy in beta-thalassemia and other maladies involving iron overload. Manipulations decreasing dietary iron should be also considered as they have been shown to modify serum ferritin levels. Thus, we hypothesized that this might reduce the exacerbation of COVID-19, especially in individuals with morbidities cursing with elevated ferritin levels such as diabetes. The biochemical parameter ferritin is involved in the dysregulation of the immune system in the hyperferritinemia condition.[6]Pro- inflammatory and direct immune-suppressive effects result in the production of a cytokine storm. The ramifications of a COVID-19 infection led to the production of a cytokine storm, and the severity of the disease depends on the cytokine storm syndrome. Raised levels of serum ferritin have been reported in diabetic patients, and it has been identified that they experience serious COVID-19 complications. They found a low number of LYM and WBC in SARS-COV-2- positive patients as compared to the NEU counts, which were elevated in these patients. In former studies, low counts of WBC and LYM have been reported in COVID-19-positive patients. Previous studies reported that COVID-19 acts on the immune cells by inhibiting cellular immune function. SARS-COV-2 propagates through the respiratory tract and involves other cells by stimulating immune responses, which change the number of WBCs, for instance, lymphocytes[7]. The primary triggering event, associated with severity and mortality has been the inflammatory cytokine storm, characterized by abrupt and excess release of pro-inflammatory cytokines including inflammatory cytokines released by macrophages particularly the interleukins IL-6, IL-10, and tumor necrosis factor (TNF-α).With this pivotal event of the pathophysiological mechanism in perspective, biochemical analysis of plasma inflammatory markers and positive acute phase reactants including ferritin could be useful for predicting the disease progression. Ferritin occurs as a cytosolic protein in most tissues, although a mitochondrial form also exists and nuclear localization has been proposed. Even though widely recognized as a representative of total body iron stores, its prognostic utility is linked with acute and chronic inflammatory processes and is nonspecifically raised in a variety of such disorders, including chronic kidney disease, rheumatoid arthritis, and autoimmune disorders,etc. In one study from China with twenty COVID-19 cases, it was found that individuals with severe diseases often present with increased serum ferritin levels, with a statistically significant difference between severe and mild categories. Whereas another study conducted using records from a large multi-hospital New York City health system demonstrated poor performance of serum ferritin for the prediction of mortality.Hyperferritinemia caused by the excessive inflammation due to the infection is associated with the admission to the intensive care unit and high mortality, and represents an indication to recognize high-risk patients to guide the therapeutic intervention to control inflammation. Serum ferritin, a feature of hemophagocytic lymph histiocytosis, which is a known complication of viral infection, is closely related to poor recovery of COVID-19 patients, and those with impaired lung lesion are more likely to have increased ferritin levels. However, these studies were performed in a relatively small sample size and/or in a single center. Thus, as a pro-inflammatory factor

in the uncontrolled cytokine storm, the predictive role of the ferritin level in the risk of poor outcome in COVID-19 patients requires further verification The laboratory tests combined with the clinical evaluation can allow a rapid assessment of the patient's condition to guide clinicians in finding the optimal approach and priority in these COVID-19 patients. Serum ferritin is particularly interesting due to its potential diagnostic and prognostic role. In this study, the current studies on COVID-19 were comprehensively investigated to determine the potential relationship of ferritin with severe condition, mortality, and other critical clinical features of COVID-19 patients.

Objectives:

- To determine the association between serum ferritin levels andCovid-19.
- To determine correlation of ferritin with severity ofCovid-19.

2. REVIEW OF LITERATURE

2.1-COVID-19:

In December 2019, a series of acute atypical respiratory disease occurred in Wuhan, China. This rapidly spread from Wuhan to other areas. It was soon discovered that a novel coronavirus was responsible. The novel coronavirus was named as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, 2019-nCoV) due to its high homology (~80%) to SARS-CoV[8], which caused acute respiratory distress syndrome (ARDS) and high mortality during 2002–2003. The outbreak of SARS-CoV-2 was considered to have originally started via a zoonotic transmission associated with the seafood market in Wuhan, China. Later it was recognized that human to human transmission played a major role in the subsequent outbreak. The disease caused by this virus was called Coronavirus disease 19 (COVID-19) and a pandemic was declared by the World Health Organization (WHO). COVID-19 has been impacting a large number of people worldwide, being reported in approximately 200 countries and territories. SARS-CoV-2 virus primarily affects the respiratory system, although other organ systems are also involved[9]. Lower respiratory tract infection related symptoms including fever, dry cough and dyspnea were reported in the initial case series from Wuhan, China. In addition, headache, dizziness, generalized weakness, vomiting and diarrhea were observed. It is now widely recognized that respiratory symptoms of COVID-19 are extremely heterogeneous[10], ranging from minimal symptoms to significant hypoxia with ARDS. In the report from Wuhan mentioned above, the time between the onset of symptoms and the development of ARDS was as short as 9 days, suggesting that there respiratory symptoms could progress rapidly[11].

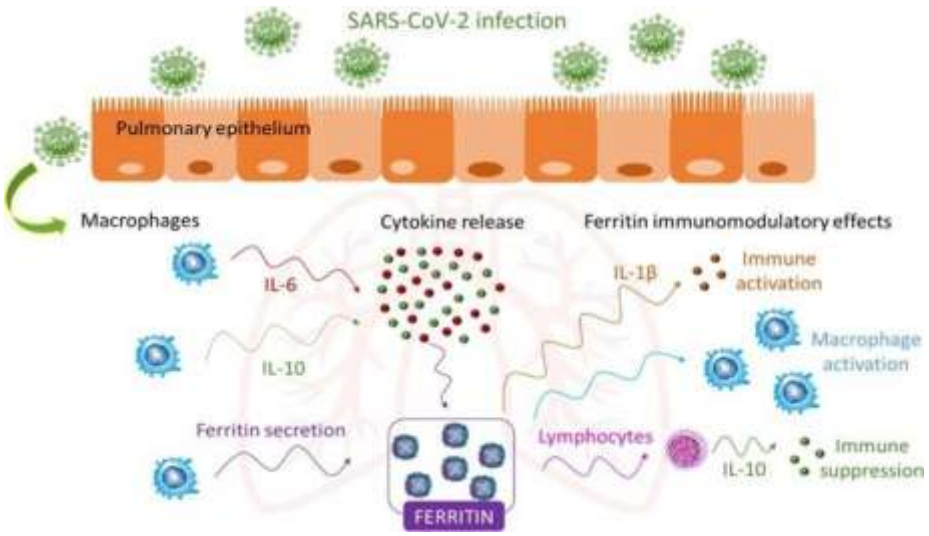


Fig.1 Potential role of ferritin during inflammation following COVID-19 infection. Active ferritin production by macrophages and cytokines may lead to hyperferritinemia, which in turn, might promote the production of several pro-inflammatory (IL-1β) and anti-inflammatory cytokines(IL-10)

2.2-Ferritin:

Ferritin, an iron storage protein, is the primary iron storage mechanism and is critical to iron homeostasis.[12]Ferritin makes iron available for critical cellular processes while protecting lipids, DNA, and proteins from the potentially toxic effects of iron[13]. Alterations in ferritin are seen commonly in clinical practice, often reflecting perturbations in iron homeostasis or metabolism. It is increasingly recognized that ferritin also plays a role in a multitude of other conditions, including inflammatory, neurodegenerative, and malignant diseases[14]. Ferritin serves as a critical component of iron homeostasis. Its primary role is in iron sequestration in which it functions as a ferroxidase, converting Fe (II) to Fe (III) as iron is internalized and sequestered in the ferritin mineral core. Ferritin is an iron-

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

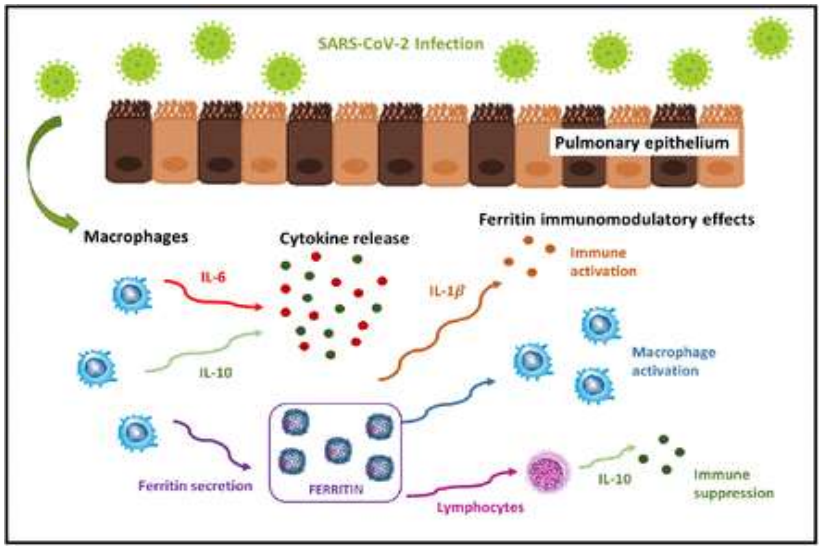
e-ISSN : 2583-1062

Impact Factor : 5.725

www.ijprems.com
editor@ijprems.com

Vol. 03, Issue 09, September 2023, pp : 379-392

binding protein that exists in both intracellular and extracellular compartments Apoferritin forms a roughly spherical container within which ferric iron is stored as a ferrihydrite mineral.[15](Apoferritin refers to the iron-free form of the protein; the iron- containing form is termed holoferritin or simply ferritin). The apoferritin shell is composed of 24 subunits. Ferritin is also key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. It has been reported that fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome,[16]thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome. Many individuals with diabetes exhibit elevated serum ferritin levels, and it is known that they face a higher probability to experience serious complications from COVID-19. On this basis, we briefly review evidence supporting the hypothesis that ferritin levels might be a crucial factor influencing the severity ofCOVID-19[17].



Ferritin role during in flammation provoked by Covid- lead to hyperferritinemia. It can induce the production of several pro-inflammatory (IL-1β) and anti-inflammatory cytokines(IL-19 infection. Active ferritin production by macrophages and cytokines may10). Illustration based on Gómez-Pastora et al. [44], Kernan and Carcillo [56], Rosário et al.

2.3-Hyperferritinemia:

Ferritin is one of the most commonly requested laboratory tests in general and secondary care, and levels deviating from reference ranges are a frequent finding. Ascribed to its proportionality to total iron stores, ferritin function is an indirect marker of iron status[18]. When concurrent inflammation is absent, ferritin has proven to be a highly specific and sensitive parameter for the diagnosis of iron deficiency. High ferritin, hyperferritinemia, may indicate increased iron stores[19], but is more commonly seen upon acute phase reactions and as a result of ferritin being released from damaged cells such as hepatocytes in liver disease. It may also be the result of increased synthesis and/or increased cellular secretion of ferritin upon various stimuli such as cytokines, oxidants, hypoxia, oncogenes, and growth factors. Ferritin reference ranges may vary according to the analytical assay being used, although upper cut off is typically set to 200 µg/L in women and 300 µg/L in men. In a prospective Danish population-based study, ferritin proved to be a strong predictor of premature death in the general population. Subjects with a baseline ferritin ≥200 µg/L were found to have increased risk of cause-specific mortality due to cancer, endocrinological disease, and cardiovascular disease, as well as increased total mortality compared to those with levels <200 µg/L. The study furthermore found a stepwise increase of this risk upon step wise increases in ferritin,with the highest cumulative risk seen upon levels ≥600µg/Clinical interpretation of hyperferritinemia often proves to be complex,and ferritin >1000 µg/L is regarded as a non-specific marker of pathology. General practitioners seem somewhat unfamiliar with the appropriate management of hyperferritinemia, as >50% of primary care patients presenting with ferritin levels of such magnitude, and without any obvious clinical reason, are not referred to secondary care nor offered any further investigation. Based on the wide etiological spectrum, hyperferritinemia should prompt for further investigation through clinical examination and additional laboratory tests when the cause remains unknown. All patients with severe COVID-19 should be screened for hyperinflammation using laboratory parameters such as ferritin which has proven to be a prognostic marker and an indicator of inflammation in these patients. Extreme hyperferritinemia with a cytokine profile similar to that seen in secondary HLH is reported in a subgroup of patients. Serial measurements of ferritin may help monitor this hyperinflammatory state and treatment response, as well as predict worsening and mortality in hospitalized COVID-19patients

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor : 5.725

www.ijprems.com
editor@ijprems.com

Vol. 03, Issue 09, September 2023, pp : 379-392

2.4-Alanine Aminotransferase and Aspartate Aminotransferase:

Clinical studies have reported that approximately 20%-30% of COVID-19 patients have liver dysfunction, which is represented by elevated levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST). Both ALT and AST are concentrated in liver, and elevations in their levels are two routinely clinical indexes indicating hepatic damage. Compared to the diffused expression of AST in other tissues as well, ALT is more specifically originated from liver. Therefore, increased ALT levels in serum have been considered more specific for liver damage than AST. Whereas in liver, AST is especially located in the zone 3 of acinus and the hepatocellular mitochondrial. Therefore, damage to zone 3, or worse hepatocyte injuries involving mitochondrial, may resulting greater elevation to AST levels.In addition to individual values of ALT and AST, the AST/ALT ratio has been explored as an important indicator for assessing liver and other diseases.[20]An elevated AST/ALT ratio might indicate alcoholic liver disease, cirrhosis and poor prognosis in acute viral hepatitis. Although higher AST levels are likely to associate with death in COVID-19 patients[21], there is still a lack of clinical studies on AST/ALT ratio to predict disease course in COVID-19 patients[22].

2.5-Urea

Blood urea nitrogen (BUN) and creatinine (Cr) are the end products of nitrogen metabolism in humans[23]. Since they are small molecules, they can be easily filtered from the nephrons. Usually, about 30% to 40% of BUN is reabsorbed from tubules, while Cr is not reabsorbed very well. Studies show that the affected neurohormonal system is responsible for the reabsorption process in patients with acute heart failure (AHF)[24]. Other studies have similarly demonstrated that the BUN/Cr ratio is more valuable than BUN or Cr alone in predicting the progression of patients with AHF. We believe that multisystem inflammation, including a cytokine storm, can occur in severe and critical groups of COVID-19 patients[25]this can in turn increase BUN reabsorption and the BUN/Cr ratio by similar mechanisms[26]. As such, this ratio would be beneficial in assessing the severity and survival of those with COVID-19 disease. In addition, there are parameters in peripheral blood whose predictive properties for COVID-19 have been demonstrated in previous studies[27]. The neutrophil-lymphocyte ratio (NLR) and C-reactive protein (CRP) make up some of these parameters[28]. In our study, we aimed to evaluate the role of applicable and cost-effective BUN/Cr ratios, as well as other routine blood parameters, to predict both the severity and survival of those with COVID-19disease[29].

2.6-Lactate Dehydrogenase (LDH):

Various biomarkers are currently under investigation for their role in determination of prognosis in patients with COVID-19[30]. Lactate dehydrogenase (LDH) is one such biomarker of interest, especially since elevated LDH levels have been associated with worse outcomes in patients with other viral infections in the past[31]. Early data in COVID-19 patients has suggested significant differences in LDH levels between patients and without severe disease[32]. Hence, we performed a pooled analysis of the published literature to explore the possible association between increased LDH values and odds of disease severity and mortality in COVID-19 patients[33].

3. MATERIALS AND METHODS

3.1 Studydesign:

Cross sectional study

Setting: Department of pathology, Benazir Bhutto Hospital, Rawalpindi.

Duration: 6 months after approval of synopsis.

Sample size: Was calculated by WHO calculation Confidence interval= 95%

Population mean= 11.7

Population standard deviation = 2.5 Absolute precision= 1

Sample size= 156

Sample technique: Non-Probability, Consecutive Sampling.

Sample Selection:

Inclusion Criteria:

- People infected withCOVID-19.
- Patients with increased level of total leucocytecount.
- Both genders will beincluded.
- Age of patients will between 18-85years.

Exclusion Criteria:

- Patients with a history of underlying medical problems like cardiovascular diseases,diabetes, chronic respiratory illness and canceretc.
- Children, Pregnant ladies and those patients who are unable to give consent willbe excluded.

3.2 Data Collection Procedure:

After taking approval from the ethical review board of my institute, a total of 156 subjects meeting inclusion criteria will be included in the study from the Department of Pathology, Benazir Bhutto Hospital, Rawalpindi. Informed written consent will be obtained. Serum ferritin level estimation will be performed on samples at room temperature 25-degree centigrade.

3.3 MATERIALS REQUIRED FORS AMPLING:

1. Gloves
2. Mask
3. Tourniquet
4. Antiseptic Solution
5. 5ml DisposableSyringe
6. Gel and Clot ActivatorTube
7. Cotton

About 3 ml blood from all the study subjects was collected in gel tubes and allowed it to clot and serum was separated from clotted sample via centrifugation at 4,000 rpm for 5 minutes. The test The method principle for measurement of Ferritin is immuno-turbidimetry using Roche kits on the Hitachi 912 clinical analyzer. Latex bound Ferritin antibodies react with the antigen in the sample to form an antigen/antibody complex. Following agglutination, this is measured turbidimetrically. Turbidity formed is proportional to the Ferritin concentration, and is measured at 700nm.

3.4 SAMPLE COLLECTION:

- First of all, I introduced myself to patient and asked for full name of the patientand checked these against requisitionform.
- Checked the requisition form for requested tests, other patient information and any special draw requirements.
- Gathered the tubes and supplies that were needed for thedraw.
- Positioned the patient in a chair, or sitting or lying on abed.
- Washed my hands and put mask and gloveson.
- Selected a suitable site for venipuncture, by placing the tourniquet 3 to 4 inches above the puncture site on thepatient.
- Did not put the tourniquet on too tightly or left it on the patient longer than 1minute.
- Disinfected the sampling site on the patient with 70% alcohol and allowed it todry.
- Inserted the needle into the vein and withdrew blood until required quantity of bloodwas obtained. Did not withdraw piston too forcefully as it could collapse thevein.
- Released tourniquet once the needle has entered thevein.
- Placed cotton immediately on the puncture site. Applied and held adequate pressureto avoid formation of hematoma.
- Then poured 3-5 ml blood in gel or clot activator tube for the estimation of ferritin, AST, ALT, urea, creatinine and LDH. Label the sample accordingly and delivered it to the lab.

3.5 SAMPLETRANSPORTATION:

Sample was transported immediately to the lab without any further delay. In case of delay,serum was stored at -20˚C.

3.6 Statistical Analysis:

Statistical analysis of data was performed by using Statistical Package for Social Sciences (SPSS) version 25. Frequency and percentage were calculated for categorical data.

3.7 Ethical Consideration:

Institutional consent was taken before the start of research work.

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor : 5.725

www.ijprems.com
editor@ijprems.com

Vol. 03, Issue 09, September 2023, pp : 379-392

4. RESULTS

Table (1): The frequency and percentage distribution of patients according to death and survivor (n=152):

	Frequency	Percent	Valid Percent	Cumulative Percent
Death	80	52.6	52.6	52.6
Survivor	72	47.4	47.4	100.0
Total	152	100.0	100.0	

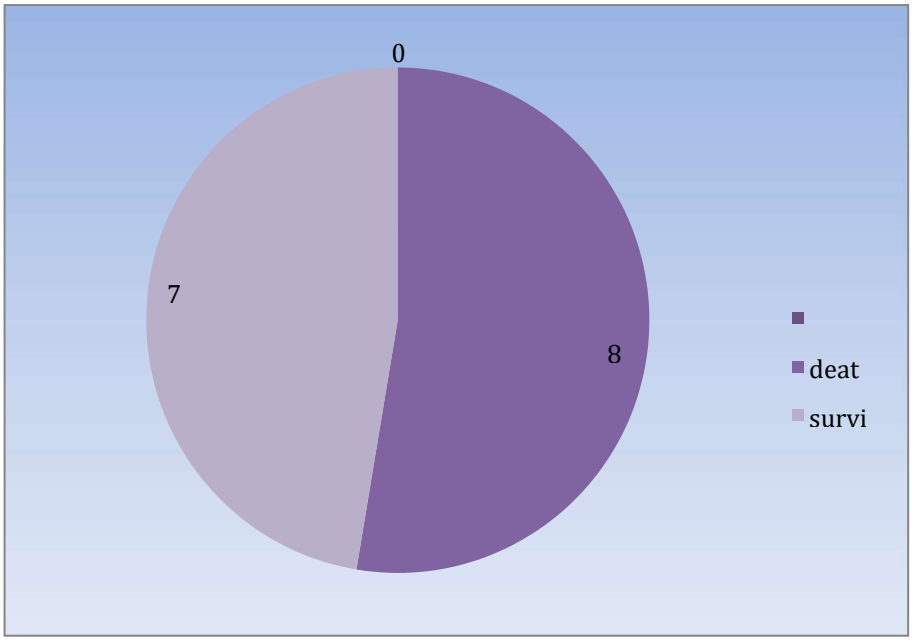


Fig (1) shows distribution according to death and survivor among patients (n=152):

Table (1.1) shows crosstabulation of age recoded and death-survivor:

Age Recoded	Death	Survivor	Total
17-34(1)	0	6	6
35-52(2)	18	22	40
53-70(3)	42	40	82
71-84(4)	20	4	24
	80	72	152

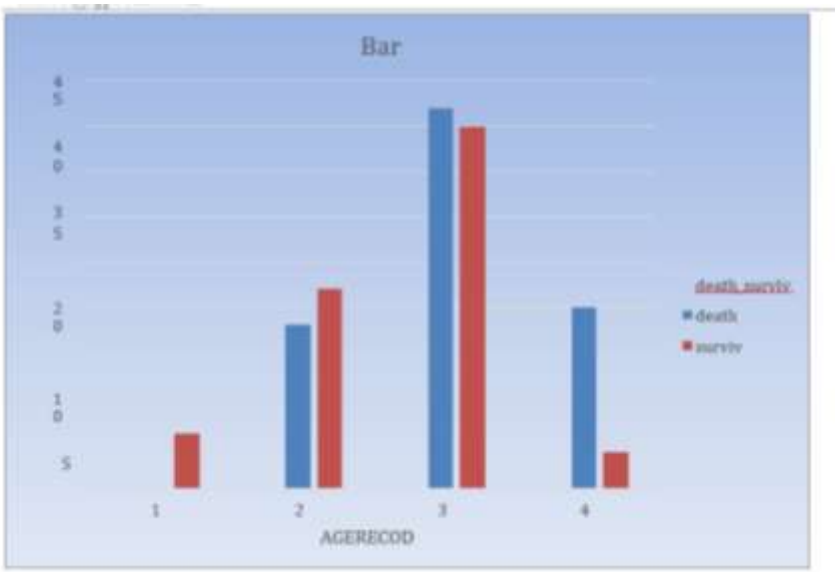


Fig (1.1) shows bar chart of age recoded and death-survivor:

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor : 5.725

www.ijprems.com
editor@ijprems.com

Vol. 03, Issue 09, September 2023, pp : 379-392

Table (2): The Frequency and percentage distribution of patients according to comorbidity (n=152):

	Frequency	Percent
No	90	59.2
Yes	62	40.8
Total	152	100.0

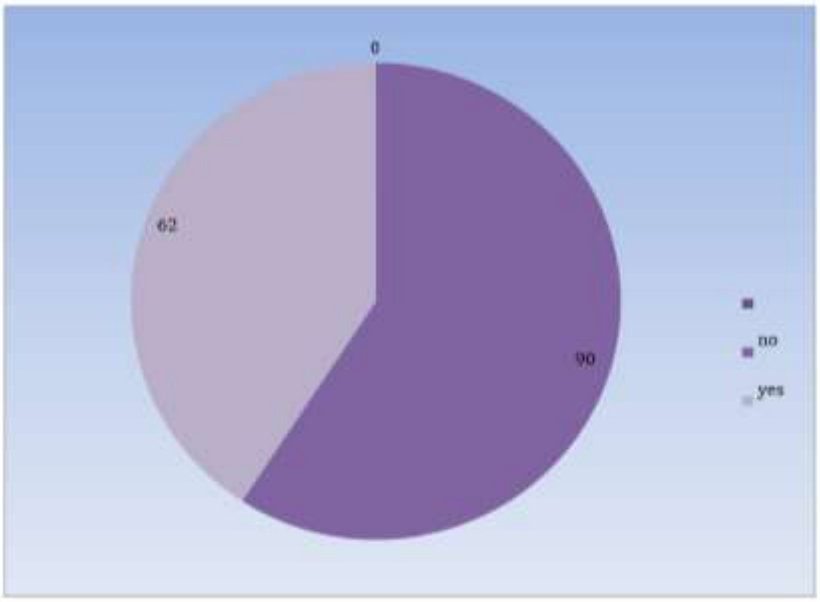


Fig (2) shows distribution of patients according to comorbidity (n=152)

Table (3): The frequency and percentage distribution of patients according to case (n=80) and control (n=72):

	Frequency	Percent
Case	80	52.6
Control	72	47.4
Total	152	100.0

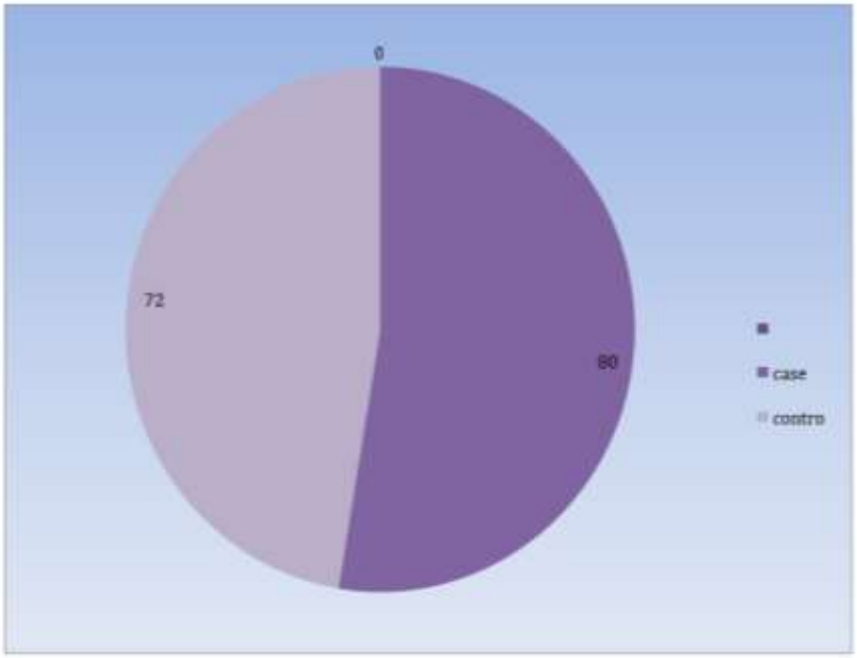


Fig (3) shows distribution of patients according to case (n=80) and control (n=72)

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

www.ijprems.com
editor@ijprems.com

Vol. 03, Issue 09, September 2023, pp : 379-392

e-ISSN : 2583-1062

Impact Factor : 5.725

Table (4) The frequency and percentage distribution according to sex (n=152)

	Frequency	Percent
Female	50	32.9
Male	102	67.1
Total	152	100.0

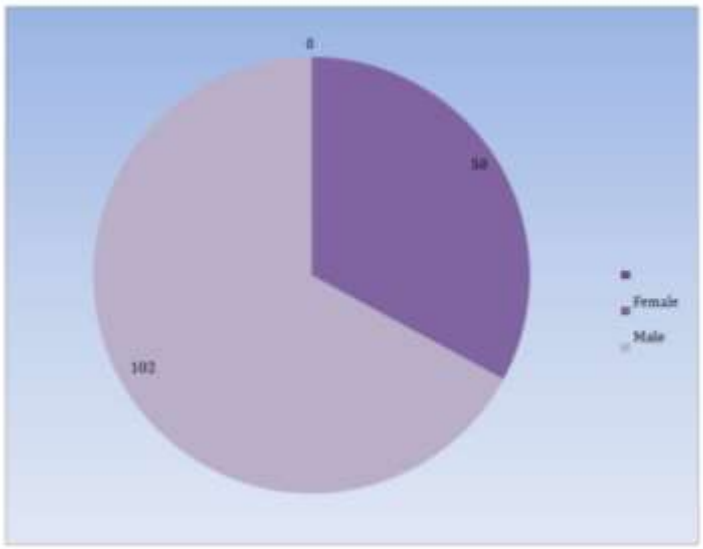


Fig (4) shows distribution according to sex (n=152)

Table (5): The Descriptive statistics of ALT, AST, LDH, creatinine, urea, ferritin and age

	Minimum	Maximum	Mean	St. Deviation
ALT	12.20	473.80	69.2145	68.83441
AST	23.70	724.70	82.5184	98.33957
LDH	169.70	1833.00	636.2276	332.76811
Creatinine	0.50	10.90	1.1899	1.34215
Urea	15.00	304.59	60.1528	45.58104
Ferritin	15.00	1000.0	533.2276	357.16664
Age	17.00	87.00	58.8684	14.41149

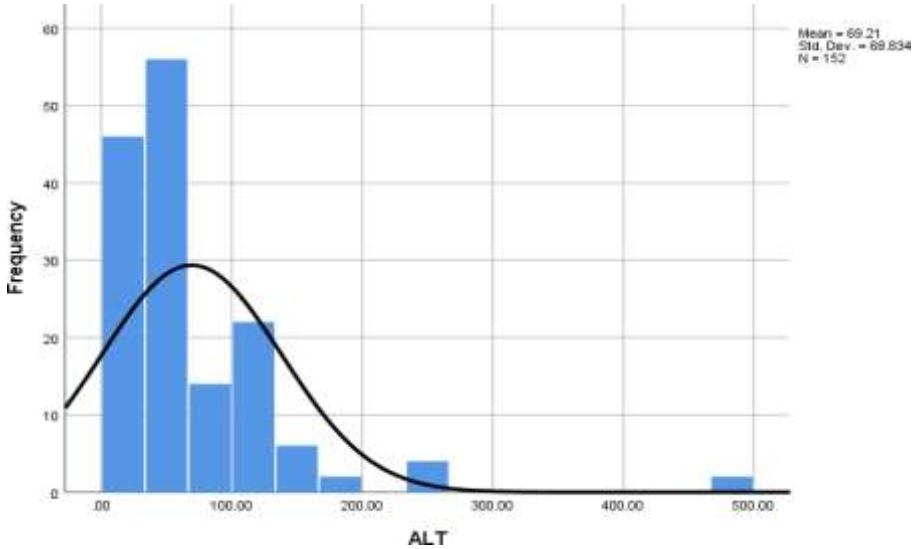


Fig (5) shows frequency distribution of ALT, AST, LDH, creatinine, urea and Ferritin

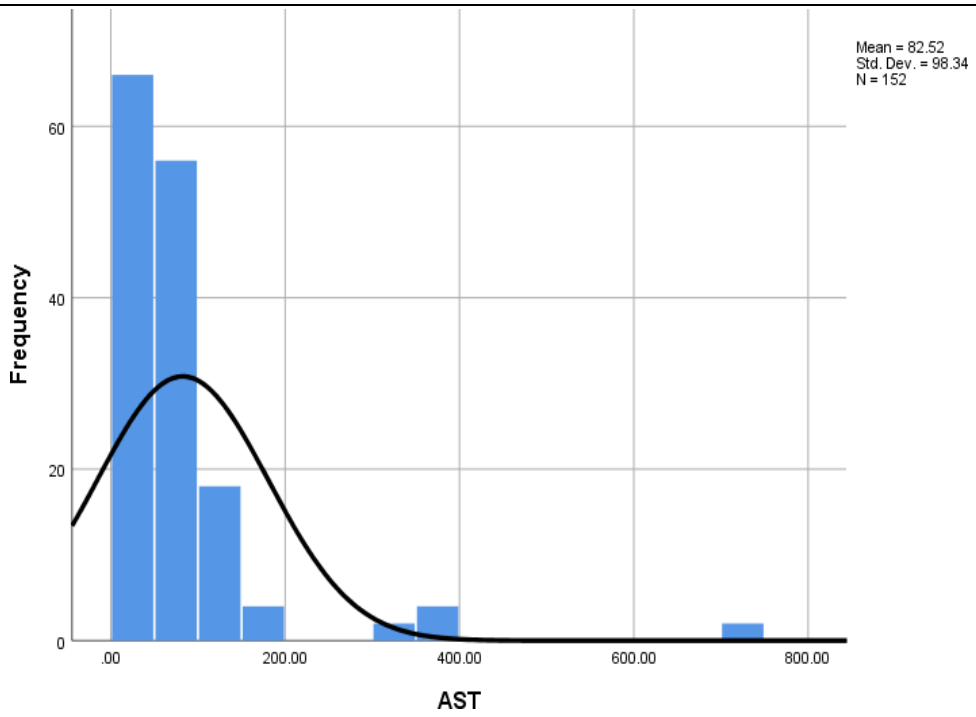
INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

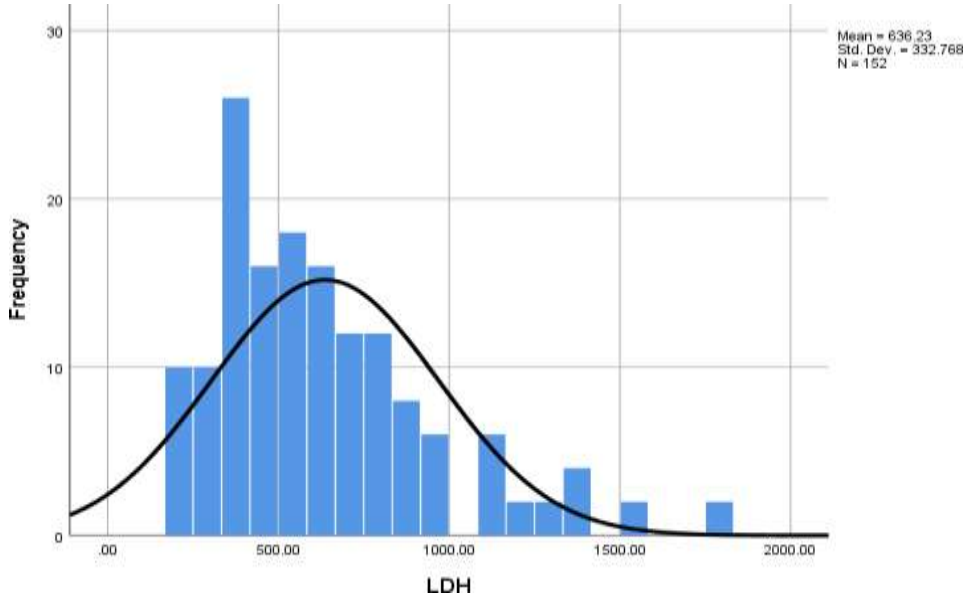
e-ISSN : 2583-1062

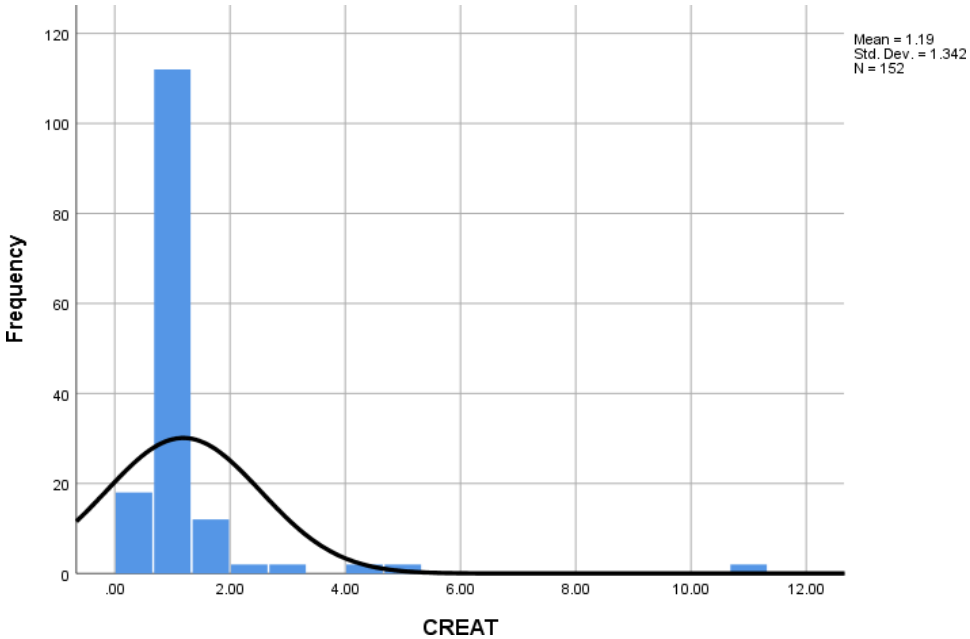
Impact Factor : 5.725

www.ijprems.com
editor@ijprems.com

Vol. 03, Issue 09, September 2023, pp : 379-392







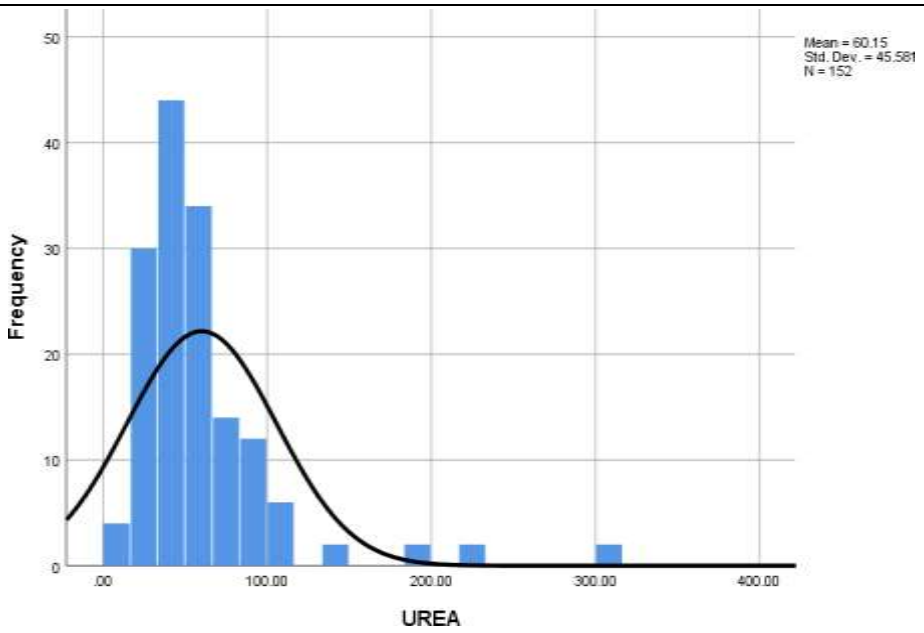
INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

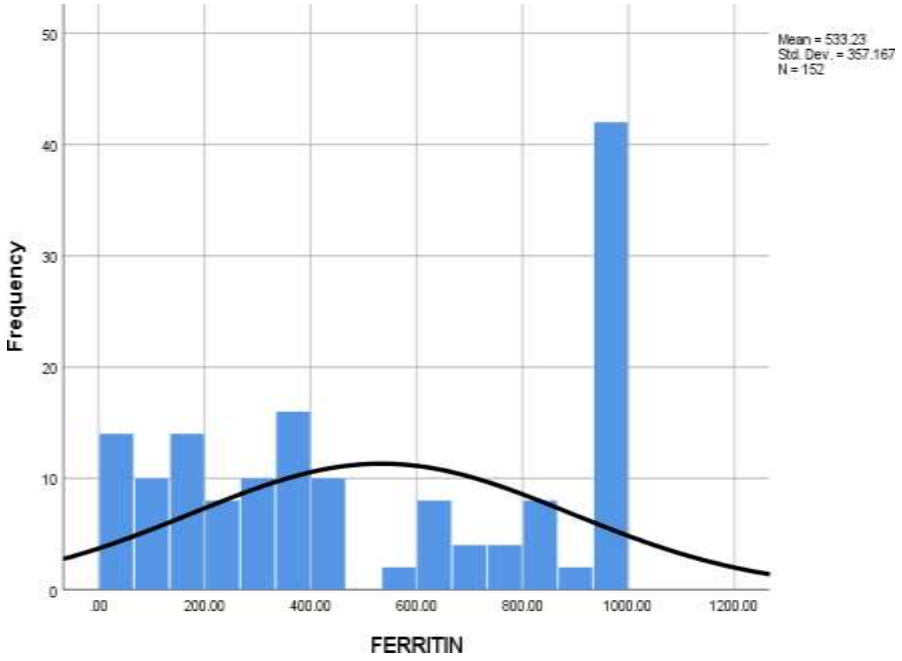
e-ISSN : 2583-1062

Impact Factor : 5.725

www.ijprems.com
editor@ijprems.com

Vol. 03, Issue 09, September 2023, pp : 379-392





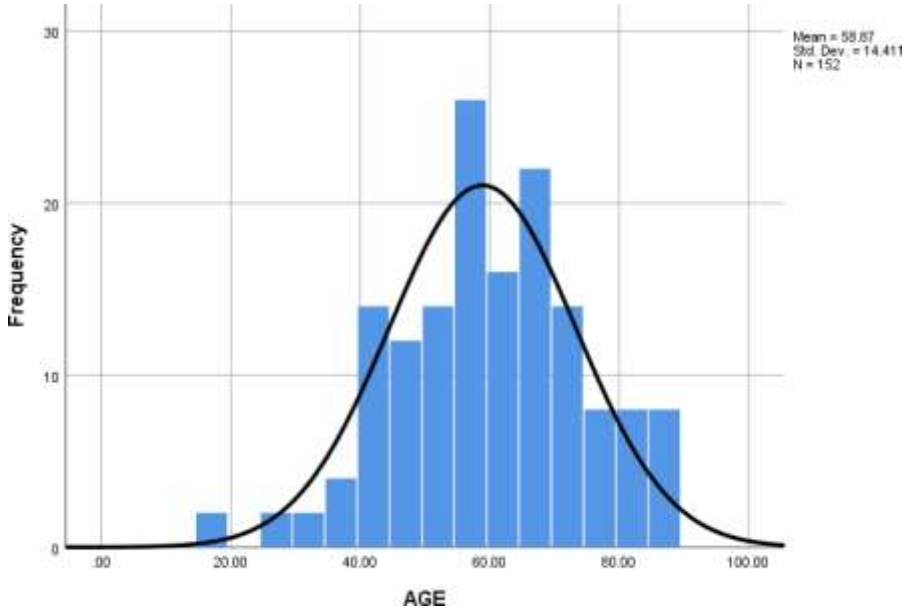


Table (6): The hypothesis of nonparametric test summary

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

e-ISSN : 2583-1062

Impact Factor : 5.725

www.ijprems.com
editor@ijprems.com

Vol. 03, Issue 09, September 2023, pp : 379-392

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of ALT is the same across categories of case_control.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.
2	The distribution of AST is the same across categories of case_control.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.
3	The distribution of AGE is the same across categories of case_control.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.
4	The distribution of LDH is the same across categories of case_control.	Independent-Samples Mann-Whitney U Test	.003	Reject the null hypothesis.
5	The distribution of CREAT is the same across categories of case_control.	Independent-Samples Mann-Whitney U Test	.789	Retain the null hypothesis.
6	The distribution of UREA is the same across categories of case_control.	Independent-Samples Mann-Whitney U Test	.906	Retain the null hypothesis.
7	The distribution of FERRITIN is the same across categories of case_control.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

5. DISCUSSION

The basic characteristics of this study showed that there were more male patients than female patients, 50 were female and 102 were male Percentage of female were 32.9 while male were 67.1 percent. This is same from Hashem's research et al. who reported that the incidence of COVID-19 was more found in men in all age groups (52.1%)[34].It is generally known that women's biological characteristics are better at producing a stronger immune response in dealing with infections including viral infections compared to men. According to population data in Makassar City in 2020, data on the number of women as many as 4.56 million residents andmen 4.50 million residents, so that in this study the number of female patients was more than male . Most of the research subjects were patients aged 41-60 years, according to a study conducted by WHO reported the average age of the COVID-19 group was 45-57 years.[35]Contrary to this study, my study revealed that people of age between 17-34 were less affected while 53-70 were severely affected. According to my study out of 152 patients 62 patients showed comorbidity with other diseases while 90 patients showed no comorbidity. Percentage of patients with comorbidity was 40.8 while those who showed no comorbidity were 59.2%. More patients with no history of comorbidities than patients with comorbidities. From 152 patients, 80 patients died of disease while 72 patients survived. Percentage of died patients were 52.6 while percentage of survival was 47.4 Less patients with mild severity than patients with severe severity, and less patients who recovered than patients who died. This is contrary to the research who found that as many as 55.2% of patients had no history of comorbidities and 44.8% had comorbidities, as well as 45.5% of patients with mild symptoms, 42.7% with moderate symptoms and 11.8% with severe symptoms. According to my study 72 were mildly ill COVID-19 patients, and 80 seriously ill COVID-19 patients, with their mean serum ferritin levels of 533.22ng/mL,which were statistically significant using the Kruskal Wallis comparison test. This is in line with the study conducted by Sonweber et al in Austria in 2020 that serum ferritin levels had a significantdifference in the severity (mild and severe) of COVID-19 Ferritin is a major mediator of immune deregulation. Inflammation caused by SARS CoV-2 can trigger an increase in ferritin production to prevent the pathogenic effect of iron. Production of active ferritin by macrophages and cytokines can cause hyperferritinemia, which will result in increased production of proinflammatory cytokines (IL-1β) and immune suppression (IL-10). Excess ferritin also contributes to the formation of Reactive Oxygen Species (ROS) which can lead to tissue damage or fibrosisThis study showed that serum ferritin levels in comorbid COVID-19 patients varied in mild severity. The lack of data specifically examines serum ferritin levels that have comorbidities on the severity of COVID-19 compared to COVID-19 patients who do not have comorbidities. However, June 2021 reported that comorbid COVID-19 patients had higher serum ferritin levels at severe than non-severe levels.

6. CONCLUSION

Covid-19 studies showed that serum ferritin was raised in severely infected patients that is why serum ferritin acts as biomarker of COVID-19 severity in hospitalized patients. Serum ferritin may be considered both the stratifying and prognostic biomarker of COVID-19.

7. LIMITATIONS

1. Sample size of current study was just 152.So there is need to conduct this study with large samplesize.
2. Short duration ofstudy
3. This study was conducted only in single Tertiary Care Hospital Rawalpindi. There isneed to conduct this study all across Pakistan.

8. REFERENCES

[1] Wang Y, Wang Y, Chen Y, Qin Q. Unique Epidemiological And Clinical Features Of The Emerging 2019 Novelcoronaviruspneumonia(Covid-19)Implicatespecialcontrolmeasures.Journalofmedicalvirology. 2020jun;92(6):568-76.

[2] Siddiqi Hk, Mehra Mr. Covid-19 Illness In Native And Immunosuppressed States: A Clinical–Therapeutic Staging Proposal. The Journal Of Heart And Lung Transplantation. 2020 May1;39(5):405-7.

[3] Rowaiye Ab, Okpalefe Oa, Adejoke Oo, Ogidigo Jo, Oladipo Oh, Ogu Ac, Oli An, Olofinase S, Onyekwere O, Abubakar Ar, Jahan D. Attenuating The Effects Of Novel Covid-19(Sars-Cov-2)

[4] Infection-Induced Cytokine Storm And The Implications. Journal Of Inflammation Research. 2021;14:1487.

[5] Kernan Kf, Carcillo Ja. Hyperferritinemia And Inflammation. International Immunology 2017 Sep;29(9):401-9.

[6] Vargas-Vargas M, Cortés-Rojo C. Ferritin Levels And Covid-19. Revista Panamericana De Salud Pública. 2020 Jun15;44:E72.

[7] Rosário C, Zandman-Goddard G, Meyron-Holtz Eg, D'cruz Dp, Shoenfeld Y. The Hyperferritinemic Syndrome: Macrophage Activation Syndrome, Still's Disease, Septic Shock And Catastrophic Antiphospholipid Syndrome. Bmc Medicine. 2013dec;11:1-1.

[8] Da Silveira Mp, Da Silva Fagundes Kk, Bizuti Mr, Starck É, Rossi Rc, De Resende E Silva Dt. Physical Exercise As A Tool To Help The Immune System Against Covid-19: An Integrative Review Of The Current Literature. Clinical And Experimental Medicine. 2021feb;21(1):15-28.

[9] Yang Cl, Qiu X, Zeng Yk, Jiang M, Fan Hr, Zhang Zm. Coronavirus Disease 2019: A Clinical Review. Eur Rev Med Pharmacol Sci. 2020 Apr1;24(8):4585-96.

[10] Kayaaslan B, Guner R. Covid-19 And The Liver: A Brief And Core Review. World Journal Of Hepatology. 2021 Dec12;13(12):2013.

[11] Perotin Jm, Gierski F, Bolko L, Dury S, Barrière S, Launois C, Dewolf M, Chouabe S, Bongrain E, Picard D, Tran E. Cluster Analysis Unveils A Severe Persistent Respiratory Impairment Phenotype 3-Months After Severe Covid-19. Respiratory Research. 2022dec;23(1):1-0.

[12] Goh Kj, Choong Mc, Cheong Eh, Kalimuddin S, Wen Sd, Phua Gc, Chan Ks, Mohideen Sh. Rapid Progression To Acute Respiratory Distress Syndrome: Review Of Current Understanding Of Critical Illness From Coronavirus Disease 2019 (Covid-19) Infection. Ann Acad Med Singapore. 2020 Mar1;49(3):108-18.

[13] Küberl A, Polen T, Bott M. The Pupylation Machinery Is Involved In Iron Homeostasis By Targeting The Iron Storage Protein Ferritin. Proceedings Of The National Academy Of Sciences. 2016 Apr26;113(17):4806-11.

[14] Kang B, Jiang D, Ma R, He H. Evidence For A Role Of Ferritin Heavy Chain In Mediating Reproductive Processes Of Geese. Reproductive Biology. 2015 Dec1;15(4):205-9.

[15] Knovich Ma, Storey Ja, Coffman Lg, Torti Sv, Torti Fm. Ferritin For The Clinician. Blood Reviews. 2009 May1;23(3):95-104.

[16] Michel Fm, Hosein Ha, Hausner Db, Debnath S, Parise Jb, Strongin Dr. Reactivity Of Ferritin And The Structure Of Ferritin-Derived Ferrihydrite. Biochimica Et Biophysica Acta (Bba)-General Subjects. 2010 Aug1;1800(8):871-85.

[17] Scaglioniv,Sorianoer.Aresuperantigensthecauseofcytokinestormandviralsepsisinseverecovid- 19? Observations And Hypothesis. Scandinavian Journal Of Immunology. 2020dec;92(6):E12944.

[18] Infante M, Pieri M, Lupisella S, D'amore L, Bernardini S, Fabbri A, Iannetta M, Andreoni M, Morello M. Low Testosterone Levels And High Estradiol To Testosterone Ratio Are Associated With Hyperinflammatorystate

[19] And Mortality In Hospitalized Men With Covid-19. European Review For Medical And Pharmacological Sciences. 2021;25(19):5889-903.

[20] Ryu Ms, Duck Ka, Philpott Cc. Ferritin Iron Regulators, Pcbp1 And Ncoa4, Respond To Cellular Iron Status In Developing Red Cells. Blood Cells, Molecules, And Diseases. 2018 Mar 1;69:75-81.

[21] Cazzola M, Bergamaschi G, Tonon L, Arbustini E, Grasso M, Vercesi E, Barosi G, Bianchi Pe, Cairo G, Arosio P. Hereditary Hyperferritinemia-Cataract Syndrome: Relationship Between Phenotypes And Specific Mutations In The Iron-Responsive Element Of Ferritin Light-Chain Mrna. Blood, The Journal Of Theamerican

[22] Society Of Hematology. 1997 Jul 15;90(2):814-21.

[23] Adams La, Angulo P. Role Of Liver Biopsy And Serum Markers Of Liver Fibrosis In Non-Alcoholic Fatty Liver Disease. Clinics In Liver Disease. 2007 Feb1;11(1):25-35.

[24] Chu H, Bai T, Chen L, Hu L, Xiao L, Yao L, Zhu R, Niu X, Li Z, Zhang L, Han C. Multicenter Analysis Of Liver Injury Patterns And Mortality In Covid-19. Frontiers In Medicine. 2020 Oct20;7:584342.

[25] Guler E, Unal Ng, Cinkooglu A, Savas R, Kose T, Pullukcu H, Harman M, Elmas Nz, Ramaiya Nh, Ozutemiz Ao. Correlation Of Liver-To-Spleen Ratio, Lung Ct Scores, Clinical, And Laboratory Findings Of Covid-19 Patients With Two Consecutive Ct Scans. Abdominal Radiology. 2021apr;46:1543-51.

[26] Lig,Gaol,Jiaj,Gongx,Zangb,Chenw.A·Lipoicacidprolongssurvivalandattenuatesacutekidney Injury In A Rat Model Of Sepsis. Clinical And Experimental Pharmacology And Physiology. 2014 Jul;41(7):459-68.

[27] Aspromonte N, Cruz Dn, Valle R, Bonello M, Tubaro M, Gambaro G, Marchese G, Santini M, Ronco C. Metabolic And Toxicological Considerations For Diuretic Therapy In Patients With Acute Heart Failure. Expert Opinion On Drug Metabolism & Toxicology. 2011 Sep1;7(9):1049-63.

[28] Ramasamy S, Subbian S. Critical Determinants Of Cytokine Storm And Type I Interferon Response In Covid-19 Pathogenesis. Clinical Microbiology Reviews. 2021 Jun16;34(3):E00299-20.

[29] Ok F, Erdogan O, Durmus E, Carkci S, Canik A. Predictive Values Of Blood Urea Nitrogen/Creatinine Ratio And Other Routine Blood Parameters On Disease Severity And Survival Of Covid-19 Patients. Journal Of Medical Virology. 2021 Feb;93(2):786-93.

[30] Anft M, Paniskaki K, Blazquez-Navarro A, Doevelaar A, Seibert Fs, Hölzer B, Skrzypczyk S, Kohut E, Kurek J, Zapka J, Wehler P. Covid-19-Induced Ards Is Associated With Decreased Frequency Of Activated Memory/Effector T Cells Expressing Cd11a++. Molecular Therapy. 2020 Dec2;28(12):2691-702.

[31] Stevens L, Pathak S, Nunes Qm, Pandanaboyana S, Macutkiewicz C, Smart N, Smith Am. Prognostic Significance Of Pre-Operative C-Reactive Protein And The Neutrophil–Lymphocyte Ratio In Resectable Pancreatic Cancer: A Systematic Review. Hpb. 2015 Apr1;17(4):285-91.

[32] Ok F, Erdogan O, Durmus E, Carkci S, Canik A. Predictive Values Of Blood Urea Nitrogen/Creatinine Ratio And Other Routine Blood Parameters On Disease Severity And Survival Of Covid-19 Patients. Journal Of Medical Virology. 2021 Feb;93(2):786-93.

[33] Wu Y, Gao J, Ji G, Feng L, Yau V, Li Y, Nanola Jp, Sun C. Periodontal Disease And Covid-19: A Systematic Review And Meta-Analysis Of Observationalstudies.

[34] Henry Bm, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, Lippi G. Lactate Dehydrogenase Levels Predict Coronavirus Disease 2019 (Covid-19) Severity And Mortality: A Pooled Analysis. The American Journal Of Emergency Medicine. 2020 Sep1;38(9):1722-6.

[35] Henry Bm, Benoit Sw, De Oliveira Mh, Hsieh Wc, Benoit J, Ballout Ra, Plebani M, Lippi G. Laboratory Abnormalities In Children With Mild And Severe Coronavirus Disease 2019 (Covid-19): A Pooled Analysis And Review. Clinical Biochemistry. 2020 Jul 1;81:1-8.

[36] Guan X, Zhang B, Fu M, Li M, Yuan X, Zhu Y, Peng J, Guo H, Lu Y. Clinical And Inflammatory Features Basedmachinelearningmodelforfatalriskpredictionofhospitalizedcovid-19patients:Resultsfroma

[37] Retrospective Cohort Study. Annals Of Medicine. 2021 Jan 1;53(1):257-66.

[38] Maghfirah Ai, Esa T, Widaningsih Y, Bahrun U. Correlation Of Serum Ferritin Levels And Covid- 19 Severity In Makassar. Journal Of Microbiology And Immunology. 2022 Jun6;4(1):1-5.

[39] Yesupatham St, Mohiyuddin Sa, Arokiyaswamy S, Brindha Hs, Anirudhpb.

[40] Estimation Of Ferritin And D-Dimer Levels In Covid-19 Patients With Mucormycosis: A Cross- Sectional Study. Journal Of Clinical & Diagnostic Research. 2022 Jan 1;16(1).