COMORBIDITIES AND FERRITIN AS OUTCOME PREDICTORS OF COVID 19 IN

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ABSTRACT

The global pandemic Corona Virus Disease 2019 (COVID-19) manifest differently in humans. Presence of comorbidities and elevated ferritin values predicts poor outcome. The study aims to find how Initial Ferritin, symptoms and comorbidities influence the patient outcome in COVID-19 positive patients. This is a retrospective observational study done among the patients diagnosed to be COVID-19 positive in the Emergency Department of a tertiary care centre in South India. Correlation between initial Ferritin to the outcome and association between respiratory symptoms and comorbidities were analysed using IBM SPSS version 20.0 software. Out of the 96 subjects, the median (Q1, Q3) initial Ferritin value among those who died was higher than those who got discharged. 65.7% of the patients with respiratory symptoms, 67.5% of diabetic patients, 71.4% of hypertensive patients, 92.9% of Chronic Obstructive Pulmonary Disease (COPD) patients, 85.7% of hypertensive patients and 90% of COPD patients who had respiratory symptoms had a prolonged hospital stay. Mortality among patient with Chronic Liver Disease (CLD) and Chronic Kidney Disease (CKD) was 62.5% and 57.1% respectively. The study concluded that there is a positive correlation

between elevated Initial Ferritin value to patient outcome in terms of mortality in COVID-19 positive patients. Presence of respiratory symptoms and comorbidities like Diabetes Mellitus, Hypertension, COPD had association with hospital stay and presence of comorbidities like CLD and CKD had association with mortality in the study population. Hence ferritin, symptoms and comorbidities can be used as outcome predictors for COVID 19.

KEYWORDS: COVID-19, ferritin, comorbidities, hospital stay, death, emergency department.

INTRODUCTION

Background/Rationale

Coronaviruses are enveloped positive- stranded Ribonucleic acid (RNA) viruses that can affect humans and animals causing severe acute respiratory syndrome. COVID-19 pandemic caused by the novel coronavirus started from a seafood market in Wuhan, a city in Hubei Province of China in December 2019. Main mode of transmission is from person to person.[1] World Health Organization (WHO) declared it as a pandemic on March 11, 2020. The first SARS-Cov-2 positive case of India was reported in Kerala on 30th January 2020. Comorbidities like Diabetes Mellitus, systemic Hypertension, Coronary Vascular disease, Chronic Obstructive Pulmonary Disease (COPD), Chronic Liver Disease(CLD), Chronic Kidney Disease(CKD) and cancer can increase the risk of complications and mortality.

Similar to other infections, the COVID-19 releases inflammatory cytokines such as Tumour Necrosis Factor Alpha(TNF-α), IL-12 (Interleukein), IL-2 and IL-8 causing Acute Respiratory Distress Syndrome (ARDS) and Multiple Organ Dysfuntion Syndrome (MODS).[2] Elevated levels of ferritin, d-dimer, lactate dehydrogenase(LDH) and IL-6 worsens the disease and increases the mortality.[3] Ferritin being a positive acute phase reactant and inflammatory marker elevates as the disease progress and the need for Intensive care unit admission.[4] Ferritin is a iron-storing protein which is also a marker of viral replication which increases as the host immunity worsens. Increased levels of ferritin is seen in conditions like HLH due to increased viral replication. The cytokines released will stimulate hepatocytes, Kuffer cells and activates macrophages, causing features of high ferritin, thrombotic storm and multi organ damage. Studies show that elevated serum ferritin seen in COVID-19 and other viral infections can cause mortality.[5] Laboratory values of such parameters are essential to classify patients based on severity and to provide targeted interventions accordingly. Cytokine storm and exaggerated host immune response causes

ARDS and respiratory failure.[6] Literature says that a ferritin of more than 500 ng/mL predicts up to 58% mortality.[7] Elevated ferritin levels can be used as a marker of poor outcome but it doesn't have prognostic importance.

Certain studies showed that the patients with associated comorbidities like Diabetes Mellitus, hypertension, dyslipidemia, CKD, CAD, COPD, liver disease, coronary artery disease showed a higher value and ferritin and higher risk for mortality in COVID-19 patients.[8] Diabetes Mellitus is associated with impaired phagocytic capabilities of T cells and elevated Angiotensin Converting Enzyme-2 (ACE-2) receptors causes entry of the virus into host cells.[9-10] The SARS-Cov-2 spike proteins attach to ACE-2 receptors and causes pre-activation thereby allowing viral entry into the host cell. Emerging data about COVID-19 suggest 8% case fatality rate in diabetic patients, with 14.2% risk for ICU admissions.[11-12] In hypertensive patients using ACE-2 inhibitors and ARBs, up regulation of ACE-2 receptors occurs(especially in the lungs) leading to increased susceptibility of SARS-Cov-2 infection, lung injury and respiratory failure. Other studies suggest that ACE-2 being a anti-inflammatory agent protects from lung injury which is inhibited by ACE inhibitors and (Angiotensin II Receptor Blocker) ARBs.[13-14] In COPD patients, increased expression of ACE-2 receptors, microbiome imbalance, susceptibility to infection, mucus production, corticosteroid use and structural damages to the airway contributes to COVID-19 illness causing hypoxia and ventilator requirement. Literature suggest 50-52.3% need for Intensive Care Unit (ICU) admission in COPD patients.[15-16] ACE-2 receptors present on the liver cells mediate the entry of SARS-Cov-2 into the hepatocytes causing increased levels of bilirubin, Serum glutamic-oxaloacetic transaminase (SGOT), Serum glutamic-pyruvic transaminase (SGPT) and LDH.[17-18] Patients with chronic kidney disease also express ACE-2 expression. SARS-Cov-2 can affect kidneys by direct cellular injury or sepsis.[19]

Objectives

The primary objective of the study is to determine the correlation between Initial Ferritin and Outcome of newly diagnosed COVID positive patient in the Emergency Department in terms of mortality. The secondary objective is to determine the association between respiratory symptoms and comorbidities to patient outcome in terms of days of hospital stay and death in newly diagnosed COVID-19 positive patient in the Emergency Department.

MATERIAL AND METHODS

Study design

A retrospective observational study done among patients diagnosed to be COVID-19 positive in the Emergency Department.

Setting

The study duration was between 10th June 2021 to 10th August 2021 in the Emergency Medicine Department of a South Indian Medical College Hospital with annual patient load of more than 25,000. The department in total has 64 beds, triage area of 36 beds, adult resuscitation area of 5 beds, neonatal resuscitation area of 1 bed, decontamination area of 2 beds, procedure room of 3 beds, Emergency critical care area of 17 beds. Either one of the COVID-19 test (SARS-CoV-2(Severe acute respiratory syndrome Coronavirus 2) antigen, Xpert SARS CoV-2, RTPCR, TrueNAT SARS CoV-2) will be performed in all the patients presenting to Emergency Department based on their symptoms and exposure history.

Participants

Patients who presented to Emergency Medicine department with various complaints and diagnosed to be COVID-19 positive regardless of age, gender, contact history were included in the study.

Exclusion criteria: Patient who were already diagnosed to be COVID-19 positive from elsewhere.

Variables: Initial ferritin value, symptoms, comorbidities like Diabetes Mellitus, hypertension, dyslipidemia, Coronary Artery Disease (CAD), COPD, Cerebrovascular Accident (CVA), CLD, CKD, cancer , duration of hospital stay in days, mortality.

Study size: Based on the mean and standard deviation of ferritin among patients diagnosed with COVID-19 (249 ±202.66) in an earlier publication (Seda Tural Onur MD, Sedat Altin MD, et. al, Could ferritin level be an indicator of COVID-19 disease mortality?. Journal of Medical Virology. 2020; 93:1672-1677) with 20% absolute error and 95% confidence the minimum sample size comes to 64. This study includes 96 patients.

Quantitative variables: Initial ferritin value in ng/ml, duration of hospital stay in days.

Statistical methods

Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables were expressed using frequency and percentage. Numerical variables were presented using mean and standard deviation. Chi-square test was used to test the statistical

significance of the comparison of symptoms, co morbidities and test findings with mortality and hospital stay. To test the statistical significance of the comparison of continuous parameters between mortality and hospital stay, Independent sample t test was used for normality and Mann Whitney U test for non normality. Pearson's correlation coefficient between ferritin and Hospital stay was calculated. A p value of <0.05 was considered to be statistically significant.

Data sources/measurement: Ferritin value was measured using Electrochemiluminescence (ECLIA). Normal Range of Ferritin was between 30-400 ng/ml.

RESULTS

Participants: All patients irrespective of their symptoms who presented to Emergency Department had to undergo one of the COVID test (SARS-CoV-2 antigen, Xpert SARS CoV-2, RTPCR, TrueNAT SARS CoV-2) as a part of hospital protocol at the time of presentation and the COVID-19 positive patients were selected for the study. SARS-CoV-2 antigen test was done for bystanders, RT-PCR was done for all regular in-patient admissions and for patients who are stable enough to wait for the results. GeneXpert SARS CoV-2 and TrueNAT SARS CoV-2 (according to availabilty) was done for patients who require ICU admissions and emergency procedures.

Study population: Patients who presented to the Emergency Department with various complaints and newly diagnosed to be COVID positive. Out of the 96 subjects 66.6% (64) were SARS-CoV-2 antigen positive, 16.7%(16) were Xpert SARS CoV-2 positive, 10.4%(10) were RTPCR (Xpert Xpress) positive, 6.3%(6) were TrueNAT SARS CoV-2 positive.

Outcome data: The median (Q1, Q3) Ferritin value among those who died was 728(390, 1619) and among those who got discharged median (Q1,Q3) Ferritin value is 309 (92.5,690) and the difference shows statistical significance with P value of 0.005. Out of the 35 patients who had respiratory symptoms 65.7%(23) had a prolonged hospital stay of more than 9 days as compared with 61 patients without respiratory symptoms 44.3%(27) had a prolonged hospital stay of more than 9 days and it is statistically significant with P value of 0.043.Out of the 40 diabetic patients, 67.5% (27) had a prolonged hospital stay (more than 9 days) as compared with 56 non diabetic patients where only 41.1%(23) had a prolonged hospital stay(more than 9days) and it is statistically significant with P value of 0.019.Out of the 35

hypertensive patients, 71.4% (25) had a prolonged hospital stay(more than 9 days) as compared with 61 patients without hypertension where only 41%(25) had a prolonged hospital stay(more than 9days) and it is statistically significant with P value of 0.004. Out of the 14 patients who had COPD, 92.9% (13)had a prolonged hospital stay (more than 9 days)as compared with 83 patients without COPD where only 45.1%(37) had a prolonged hospital stay (more than 9 days) and it is statistically significant with P value of 0.003. Out of the 14 hypertensive patients who had respiratory symptoms, 85.7% (12) patients had a prolonged hospital stay (more than 9days) as compared with other 82 patients where only 46.3% (38) had a prolonged hospital stay(more than 9days) and it is statistically significant with P value of 0.015.Out of the 10 COPD patients who had respiratory symptoms, 90.0% (9) patients had a prolonged hospital stay (more than 9days) as compared with 86 other patients where only 47.7% (41) had a prolonged hospital stay(more than 9days) and it is statistically significant with P value of 0.028. Out of the 8 patients who had CLD, 62.5% (5) patients expired as compared with the mortality in patients without CLD 11.1% (8) and it is statistically significant with P value of 0.001.Out of the 7 patients who had CKD, 57.1% (4) patients expired as compared with the mortality in patients without CKD 12.3% (9) and it is statistically significant with P value of 0.011.

Main results

Table no. 1: Demographics of newly diagnosed COVID-19 patients.

Variables		Frequency n	Percentage %
Gender	Male	51	53.1
	Female	45	46.9
Covid symptoms	Present	72	75
	Absent	24	25
Contact history	Present	28	29.1
	Absent	68	70.9
Admission status	Home quaratine	16	16.7
	Admitted	80	83.3

The present study contains 96 subjects of which 46.9%were females (45) and 53.1% were males (51). Mean age of presentation was 49.76 ± 10.043.

Out of the total number of COVID positive patients 29.1% (28) had contact with COVID positive patient and the rest 70.9%(68)had no contact history.25%(24) of patients were asymptomatic and 75% (72)were symptomatic.

Out of the 96 patients 16.7% (16) patients went for home quarantine and the rest got admitted out of which 69.8%(67) got discharged 13.5%(13) died of the disease.
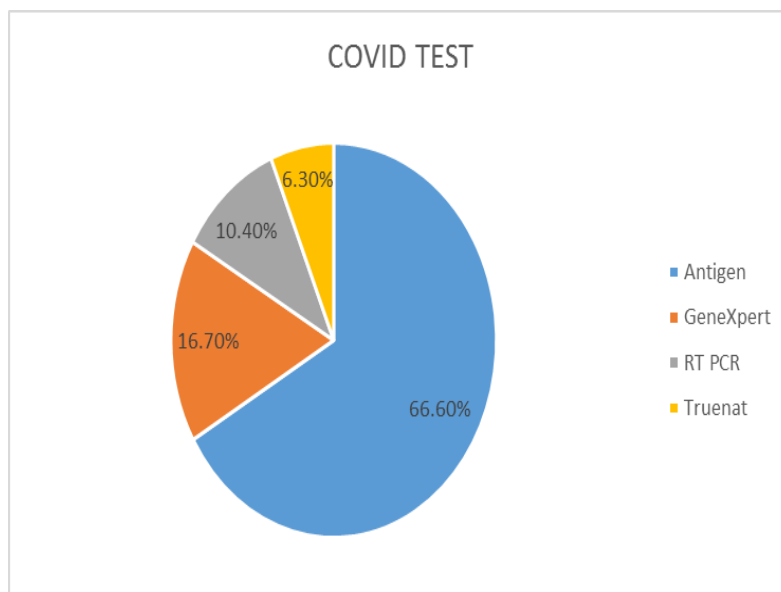

Figure no. 1: Distribution based on COVID test.

66.6% (64) were antigen positive, 16.7%(16) were Gene Xpert positive, 10.4%(10) were RTPCR positive, 6.3%(6) were Truenat positive.
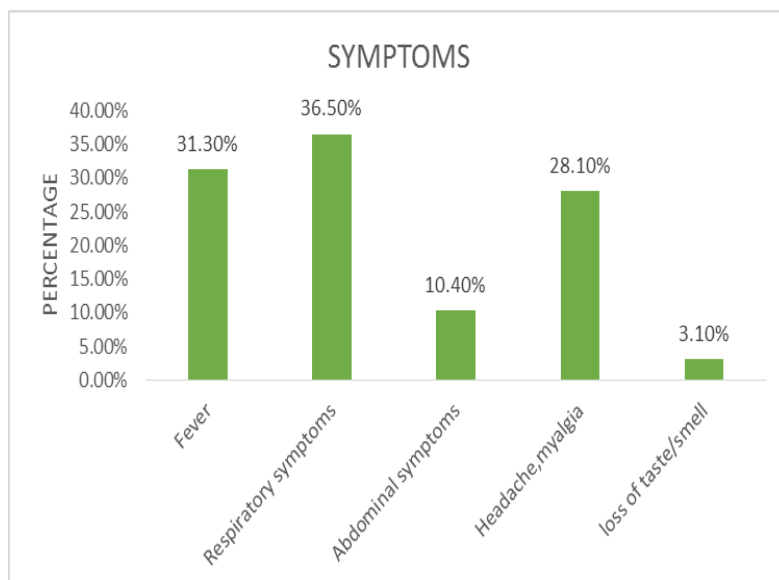

Figure no. 2: Distribution based on symptoms.

Out of the total number of patients 31.3%(30) had fever, 36.5%(35) had respiratory symptoms like cough and breathlessness, 10.4%(10) had abdominal symptoms like diarrhea, vomiting, abdominal discomfort, 28.1%(27) had either as headache or myalgia, 3.1%(3)had either aguesia (loss of taste) or anosmia(loss of smell).
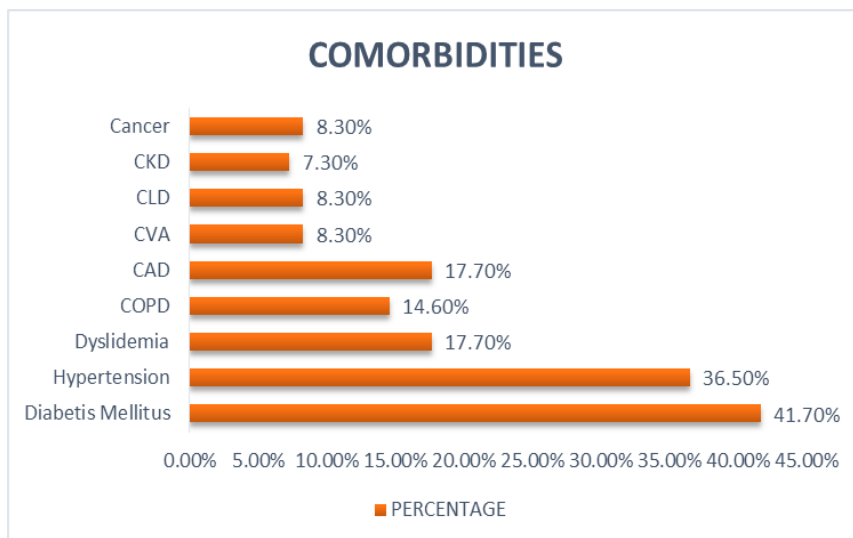
Figure no. 3: Distribution based the comorbidities of the patients.

Out of the total number of patients 41.7%(40) were diabetic, 36.5%(35) were hypertensive, 17.7%(17) had dyslipidemia, 14.6%(14) had COPD, 17.7%(17) had Coronary Artery Disease, 8.3%(8)had a past history of CVA, 8.3%(8) had CLD, 7.3%(7) has CKD and 8.3%(8) had cancer.
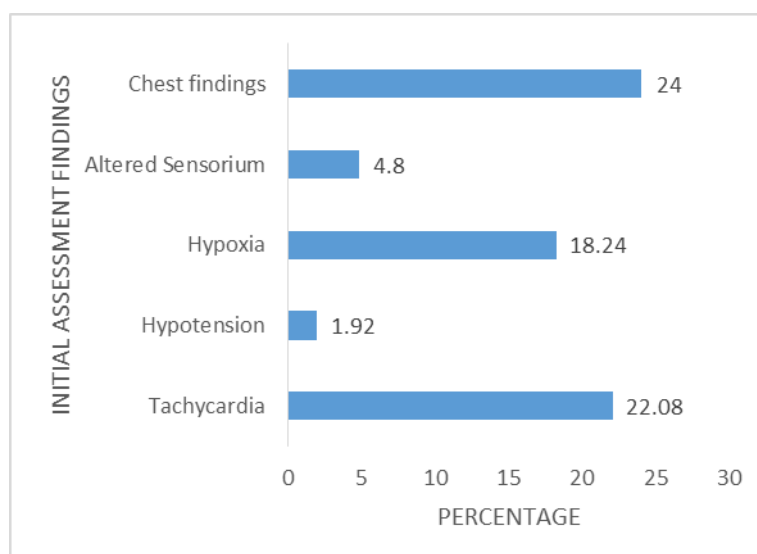

Figure no. 4: Distribution based on initial assessment findings.

Out of the 96 patients, 24% (23) had chest findings at the time of presentation to the Emergency Department. 22.08% (23) were having tachycardia at the time of presentation. 1.92% (2) had a MAP <65mmHg at the time of presentation. 18.24% (19) had hypoxia and 4.8% (5) had altered sensorium at the time of presentation.

Table no. 2: Comparison of Ferritin values based on the patient Outcome.

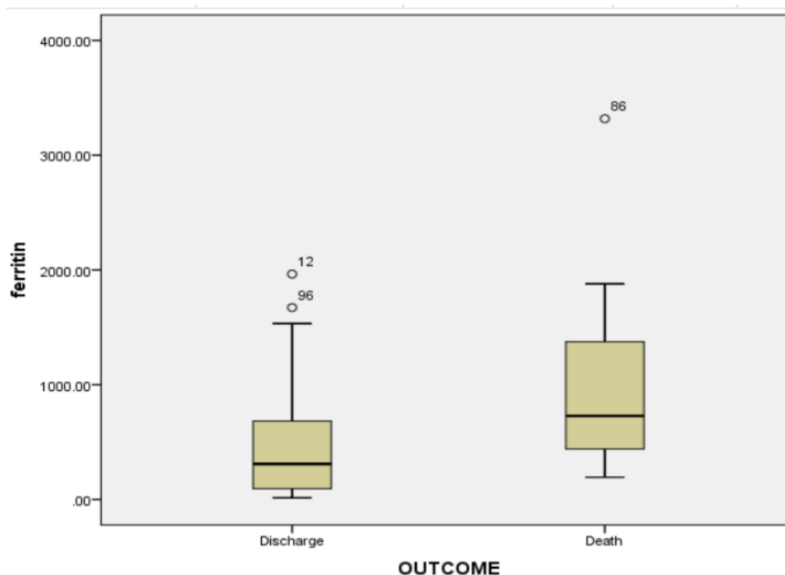| Outcome	N	Median ferritin	(q1,q3)	P value
Discharge	67	309	92.5,690	0.005
Death	13	728	390,1619	

Figure no. 5: Box plot representing the Comparison of Ferritin values of based on the patient Outcome.

The comparison of median (Q1, Q3) Ferritin value among those who died (13) was 728(390, 1619) and among those who got discharged (67) was 309 (92.5,690). The comparison of ferritin with patient outcome in terms of mortality is statistical significant with p value 0.005.

Association of Symptoms and Comorbidities with length of hospital stay

Table no. 3: Association of symptoms and comorbidities with length of hospital stay.

Variables		Hospital stay		P value
		Less than 9 days N (%)	More than or equal to 9 days N (%)	
Respiratory symptoms	Absent (n=61)	34(55.7)	27(44.3)	0.043
	Present (n=35)	12(34.3)	23(65.7)	
Diabetes mellitus	Absent (n=56)	33(58.9)	23(41.1)	0.019
	Present (n=40)	13(32.5)	27(67.5)	
Hypertension	Absent (n=61)	36(59)	25(41)	0.004
	Present (n=35)	10(28.6)	25(71.4)	
Hypertension with respiratory symptoms	Absent (n=82)	44(53.7)	38(46.3)	0.015
	Present (n=14)	2(14.3)	12(85.7)	
Copd	Absent (n=82)	45(54.9)	37(45.1)	0.003
	Present (n=14)	1(7.1)	13(92.9)	

Copd with respiratory symptoms	Absent (n=86)	43(52.3)	41(47.7)	0.028
	Present (n=10)	1(10)	9(90)	

Out of the 61 patients who didn't have respiratory symptoms, 34(55.7%) had a hospital stay of less than 9 days and 27(44.3%) had a hospital stay of more than 9 days. Out of the 35 patients who had respiratory symptoms, 12(34.3) had a hospital stay less than 9 days and 23(65.7%) had a hospital stay of more than 9 days. Association of Respiratory symptoms with the length of hospital stay is statistically significant with p value 0.043.

Out of the 56 patients who were not diabetic, 33(58.9%) had a hospital stay of less than 9 days and 23(41.1%) had a hospital stay of more than 9 days. Out of the 40 patients who were diabetic, 13(32.5%) had a hospital stay less than 9 days and 27(67.5%) had a hospital stay of more than 9 days. Association of Diabetes Mellitus with the length of hospital stay is statistically significant with p value 0.019.

Out of the 61 patients who were not hypertensive, 36(59%) had a hospital stay of less than 9 days and 25(41%) had a hospital stay of more than 9 days. Out of the 35 patients who were hypertensive, 10(28.6%) had a hospital stay less than 9 days and 25(71.4%) had a hospital stay of more than 9 days. Association of Hypertension with the length of hospital stay is statistically significant with p value 0.004.

Out of the 82 patients who were not hypertensive nor having respiratory symptoms, 44 (53.7%) had a hospital stay of less than 9 days and 38(46.3%) had a hospital stay of more than 9 days. Out of the 14 patients who were hypertensive and who had respiratory symptoms, 2(14.3%) had a hospital stay less than 9 days and 12(85.7%) had a hospital stay of more than 9 days. Association of Hypertension patients with respiratory symptoms based on the length of hospital stay is statistically significant with p value 0.015.

Out of the 82 patients who were not having COPD, 45(54.9%) had a hospital stay of less than 9 days and 37(45.1%) had a hospital stay of more than 9 days. Out of the 14 patients who had COPD, 1(7.1%) had a hospital stay less than 9 days and 13(92.9%) had a hospital stay of more than 9 days. Association of COPD with the length of hospital stay is statistically significant with p value 0.003.

Out of the 86 patients who were not having COPD with respiratory symptoms, 43(52.3%) had a hospital stay of less than 9 days and 41(47.7%) had a hospital stay of more than 9 days. Out of the 10 COPD patients who had respiratory symptoms, 1(10%) had a hospital stay less than 9 days and 9(90%)had a hospital stay of more than 9 days.Association of COPD with respiratory symptoms based on the length of hospital stay is statistically significant with p value 0.028.

Association of comorbidities with mortality

Table no. 4: Association of comorbidities with mortality.

Variables		Discharge N (%)	Death N (%)	P value
Cld	Absent (n=72)	64(88.9)	8(11.1)	0.001
	Present (n=8)	3(37.5)	5(62.5)	
Ckd	Absent (n=73)	64(87.7)	9(12.3)	0.011
	Present (n=7)	3(42.9)	4(57.1)	

Out of the 72 patients who were not having CLD, 64(88.9%) were discharged and mortality was for 8(11.1%). Out of the 8 patients who had CLD, 3(37.5%) were discharged and mortality was for 5(62.5%). Association of CLD with mortality is statistically significant with p value 0.001.

Out of the 73 patients who were not having CKD, 64(87.7%) were discharged and mortality was for 9(12.3%). Out of the 7 patients who had CKD, 3(42.9%) were discharged and mortality was for 4(57.1%). Association of CKD with mortality is statistically significant with p value 0.011.

DISCUSSION

Key results: In our study done among newly diagnosed COVID-19 positive patients there is a positive correlation between elevated Initial Ferritin value to patient outcome in terms of mortality. Presence respiratory symptoms and comorbidities like Diabetes Mellitus, hypertension, chronic obstructive pulmonary disease had a positive correlation with hospital stay and presence of comorbidities like chronic liver disease and chronic kidney disease had a positive correlation with mortality. Therefore presence of respiratory symptoms, comorbidities and elevated initial ferritin can be used as a predictor of poor patient outcome. The hospital stay of diabetic patients were prolonged since they are prone for other associated infections because of uncontrolled blood sugars secondary to COVID-19 infection and use of steroids. Since COPD patients have poor respiratory reserve, they are more prone for

respiratory infections and were observed to have prolonged hospital stay. Since CLD patients are at risk of hepatic decompensation secondary to infections mortality rate was more in them. Sepsis induced worsening of renal funtions in patients with CKD lead to increased mortality in this group of patients.

Limitations

The major limitation was that the study was conducted in a single centre. We would recommend a multicentre study with a larger number of recorders and interpreters for further validation. The association between initial vitals, other symptoms other than respiratory symptoms, Chest X-ray and other laboratory findings with the patient outcome has not been discussed here. Comorbidities like cancer which had a positive correlation with the poor patient outcome in COVID-19 infection in other studies was not observed here since the number of cancer patients were less. The correlation between the ferritin value to the comorbidities were not discussed in this study. Hospital acquired infections secondary to COVID 19 infections which may contribute to prolonged hospital stay and mortality was not discussed here.

CONCLUSION

The study concludes that there is a positive correlation between elevated Initial Ferritin value to patient outcome in terms of mortality in COVID-19 positive patients. Presence of respiratory symptoms and comorbidities like Diabetes Mellitus, Hypertension, COPD had a positive association with hospital stay and presence of comorbidities like CLD and CKD had a positive association with mortality in the study population. Hence ferritin, symptoms and comorbidities can be used as outcome predictors for COVID 19.

Other information

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Research Quality and Ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require the Institutional Review Board / Ethics Committee review (ECASM-AIMS-2021-224, 18/5/2021). We also

certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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