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Original Article

Biochemistry Section

Association of Serum Calcium and Serum Uric Acid Level with Inflammatory Markers to Predict the Outcome of COVID-19 Infection: A Retrospective Study

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ABSTRACT

Introduction: Novel Coronavirus Disease 2019 (COVID-19) is an acute respiratory disease and the severity of COVID-19 is highly variable, ranging from asymptomatic infection to life-threatening disease. Therefore, biomarkers are required to assess the prognosis of the disease at the earliest.

Aim: To determine the correlation of serum calcium and serum uric acid levels with inflammatory markers of COVID-19 infection and also to assess serum calcium and serum uric acid levels in predicting the outcome of COVID-19 infection.

Materials and Methods: A retrospective study was conducted in Adichunchanagiri Institute of Medical Sciences, B.G Nagara, Karnataka, India from 1st April 2021 to 30th June 2021. Out of 483 COVID-19 infected patients admitted during the study period, data of 136 patients, investigated for serum calcium and serum uric acid levels were collected from medical records. Patients were categorised into survived and non survived group based on the outcome. Descriptive statistics, Analysis of Variance (ANOVA) test, Student's t-test were applied. Receiver Operating Characteristic (ROC) curve was used in predicting the outcome of COVID-19 infection.

Results: Of the 136 COVID-19 positive patients, 87 were male and 49 were female patients. Mean age of non survived was significantly higher (59.19±12.6 years) as compared to survived patients (44.44±13.35 years). Further, Random Blood Sugar (RBS), C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH) and D-dimer values were significantly higher among non survived patients (233±135.37 mg/dL, 9.92±3.93 mg/L, 422.88±191.51 IU/L and 586.19±258.9 ng/mL, respectively) as compared to survived patients. Significant positive correlation was found between serum uric acid levels with LDH (r-value=0.231; p-value=0.007). Whereas, serum calcium showed negative correlation with CRP (r-value=-0.55; p-value=0.526) and D-dimer (r-value=-0.052; p-value=0.551). The ROC curve analysis showed that area under curve for serum uric acid level (0.530) was more as compared to serum calcium (0.460).

Conclusion: Serum uric acid is emerged as a better biomarker towards the prediction of outcome of patients. Early evaluation of serum calcium levels and serum uric acids could aid in predicting the outcome of the disease.

Keywords: Biomarkers, Coronavirus disease 2019, Receiver operating characteristic, Severity

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) predominantly affects respiratory system and may manifest from asymptomatic to mild symptoms or severe respiratory disease [1]. In early December 2019, the first case of pneumonia of unknown origin was identified in Wuhan, the capital city of Hubei province [2]. From then COVID-19 quickly spread throughout the world and World Health Organisation (WHO) has declared it as a pandemic [3]. In India, from 3rd January 2020 to 7th June 2021, there have been 28,909,975 confirmed cases of COVID-19 with 349,186 deaths reported [4].

During the first wave of COVID-19 pandemic many studies were undertaken to investigate the clinical and laboratory characteristics [5-7]. The commonly investigated parameters were routine biochemical and pathological investigation, inflammatory markers, organ injury biomarkers and CT scan of thorax [1,8]. However, very few studies are conducted on serum calcium levels in COVID-19 infection [9,10].

Many theories have been put across to explain the clinical manifestations and severity of COVID-19 infection. However, the pathogenesis of COVID-19 is not clear and also there is currently no effective antiviral treatment [11]. During the second wave, the altered serum calcium level and serum uric acid levels in severely infected hospitalised COVID-19 patients were observed by the researchers [9,11].

Several potential factors play an important role in causing hypocalcaemia in COVID-19. One could be a direct effect of SARS-CoV-2 viral E gene entry into host cells [12-14]. SARS-CoV-2 viral E gene encodes a small transmembrane protein that functions as a calcium ion channel and causes alteration in calcium homeostasis within the host cell leading to the activation of inflammatory pathways resulting in lung cell damage. As a whole formation of virus structure, its entry into host cell, replication and their virion release, requires calcium [15]. Serum uric acid is a strong reactive oxygen species and being an antioxidant plays important role in defence mechanism [16,17]. Schuler CF et al., showed that when the virus enters the body it invades the respiratory system and causes inflammation that results in increase in serum uric acid level [18].

Kelly A and Levine MA reported that acutely ill patients had decreased levels of serum calcium which is associated with a poor prognosis [10]. A retrospective analysis by Zheng T et al., reported that the serum uric acid level was positively associated with inflammatory markers [19]. In contrary, Hu F et al., in their study on association of serum uric acid levels with COVID-19 severity reported that serum uric acid and serum uric acid/creatinine levels at admission were lower in patients with severe COVID- 19 as compared to moderately infected patients [11].

The relation between serum uric acid levels with severity of COVID-19 infection is inconsistent. Further no studies have compared the

serum calcium and serum uric acid level with outcome of COVID-19 infection. Early initiation of therapy according to alterations in serum calcium level and serum uric acid level may decrease the mortality of COVID-19 infection. Hence, the aim of the present study was to check the correlation between serum calcium and serum uric acid level with inflammatory makers among COVID-19 patients and to assess serum calcium and serum uric acid levels in predicting the outcome of COVID-19 infections.

MATERIALS AND METHODS

This retrospective study was conducted in Adichunchanagiri Institute of Medical Sciences (AIMS), B.G Nagara, Karnataka, India. The data of COVID-19 patients admitted at AIMS from 1st April 2021 to 30th June 2021 was collected from medical records for a period of two months and was analysed between October 2021 to November 2021. Study was initiated after obtaining ethical clearance from Institutional Ethical Committee [No. AIMS/IEC/261/2021 Dated18/06/2021].

Inclusion criteria: COVID-19 patients, confirmed with Rapid Antigen Test (RAT) and/or Real Time Polymerase Chain Reaction (RT-PCR), aged >18 years, who were investigated for calcium and serum uric acid level either on the day of admission or during their stay in the hospital were included in the study.

Exclusion criteria: Patients who had history of parathyroid disease, bone disease, chronic liver disease, kidney dysfunction and malignant tumours were excluded from the study.

During the study period, 483 COVID-19 infected patients were admitted at AIMS, out of which, 136 COVID-19 patients, investigated for calcium and serum uric acid level were enrolled in the study by convenient sampling method.

Data Collection

The data required for the present study was obtained from the medical records. Data included baseline clinical characteristics like age, gender, co-morbid status, duration of hospital stay and investigations such as Random Blood Sugar (RBS), blood urea, serum creatinine, serum albumin, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), Alkaline Phosphatase (ALP), serum calcium, serum uric acid, C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH) was analysed by various methods using Vitros-250 dry chemistry and D-dimer was analysed using XL 1000i operan, done on the day of admission and or during the stay were included. Above mentioned biochemical investigations were analysed for COVID-19 infected patients as these are inflammatory markers and are associated with severity and mortality of COVID-19 disease [5-7].

All the COVID-19 patients were categorised into survived and non survived group, based on their serum calcium levels patients were grouped into normal (8.5-11 mg/dL) or decreased (<8.5 mg/dL) and based on their serum uric acid level patients were divided into three groups normal (2.5-6 mg/dL), decreased (<2.4 mg/dL) or increased (>6 mg/dL) [Table/Fig-1] [20].

STATISTICAL ANALYSIS

The collected data was entered in Microsoft excel sheet and analysed using Epi data software. Descriptive statistics like frequency and proportion was calculated. Student's t-test was used and p-value <0.05 was considered as statistically significant. Analysis of Variance (ANOVA) test was used to compare the parameters with different levels of serum uric acid. Pearson's correlation was employed to examine the correlation between serum calcium level and serum uric acid level with outcome of COVID-19 admitted patients. Receiver Operating Characteristic (ROC) curve was used to assess serum calcium and serum uric acid in predicting the development of outcome of COVID-19 infection.

Biochemical parameters	Reference range*	Method of analysis
RBS	70-150 mg/dL	Dry chemistry
Blood urea	15-50 mg/dL	
Serum creatinine	0.4-1.4 mg/dL	
Serum albumin	3.5-5.2 g/dL	
AST	up to 31 U/L	
ALT	up to 31 U/L	
ALP	110-360 U/L	
Serum Calcium	8.5-11 mg/dL	
Serum Uric Acid	2.5-6 mg/dL	
CRP	0-6 mg/L	
LDH	80-285 IU/L	
D-dimer	up to 500 ng/mL	Fluorescence immunoassay

[Table/Fig-1]: Reference ranges for biochemical parameters.
RBS: Random blood sugar; AST: Aspartate amino transferase; ALT: Alanine amino transferase; ALP: Alkaline phosphatase; CRP: C-reactive protein; LDH: Lactate dehydrogenase.
*According to Vitros-250 dry chemistry and XL 1000i operan kit insert

RESULTS

Among 136 COVID-19 positive patients, 87 (76 survived and 11 non survived) were male patients with mean age of 47.10±14.48 years and 49 (34 survived and 15 non survived) were female patients with mean age of 47.53±14.4 years and there was no significant difference between the gender with p-value of 0.86.

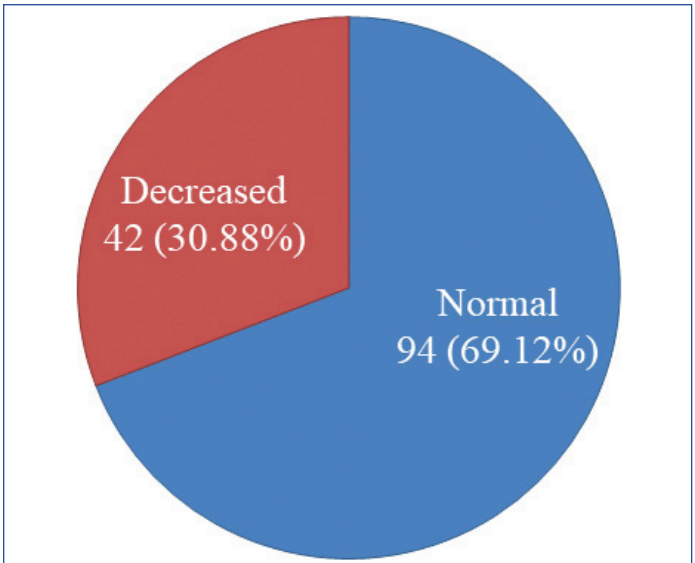
The mean age of non survived was significantly higher as compared to survived patients. Further, RBS (p-value=0.013), CRP (p-value=0.023), LDH (p-value=0.010) and D-Dimer (p-value=0.043) values were higher among non survived patients as compared to survived patients and it was found be significant. Whereas mean values of albumin (p-value=0.014) were higher among survived patients as compared to non survived with significant difference between them [Table/Fig-2].

Parameters	Survived group (Mean±SD)	Non survived group (Mean±SD)	p-value
Age (years)	44.44±13.35	59.19±12.6	0.0001*
RBS (mg/dL)	171.95±104.10	233±135.37	0.013*
Blood urea (mg/dL)	30.02±17.85	37.73±18.41	0.051
Serum creatinine (mg/dL)	0.95±0.55	0.92±0.560	0.794
Serum albumin (g/dL)	3.75± 0.51	3.46±0.647	0.014*
AST (U/L)	56.04±45.0	55.62±33.281	0.964
ALT (U/L)	52.27±53.36	47.96±26.197	0.690
ALP (U/L)	102.29±48.34	110.96±85.89	0.489
Serum calcium (mg/dL)	8.85±0.91	8.69±1.16	0.439
Serum uric acid (mg/dL)	4.086±1.56	4.39±1.88	0.402
CRP (mg/L)	8.12±3.53	9.92±3.93	0.023*
LDH (IU/L)	334.04±146.20	422.88±191.51	0.010*
D-dimer (ng/mL)	491.66±200.05	586.19±258.9	0.043*

[Table/Fig-2]: Comparison of the parameters among survived and Non survived group.
RBS: Random blood sugar; AST: Aspartate amino transferase; ALT: Alanine amino transferase; ALP: Alkaline phosphatase; CRP: C-reactive protein; LDH: Lactate dehydrogenase; SD: Standard deviation; *p-value <0.05 was considered statistically significant (Student's t-test)

As seen in [Table/Fig-3], out of 136 COVID-19 positive patients, 94 (69.12%) had normal serum calcium level with mean value of 9.30±0.56 mg/dL and 42 (30.88%) patients had decreased serum calcium level with mean value of 7.81±0.72 mg/dL and it was found to be statistically significant (p-value <0.0001).

D-dimer level was significantly higher among patients with decreased calcium level as compared to patients with normal calcium level. However, other parameters like RBS, urea, creatinine, AST, ALT, ALP, CRP and LDH values were higher among patients with decreased calcium level. Whereas, Albumin and serum uric acid level was lower among patients with decreased calcium level [Table/Fig-4].

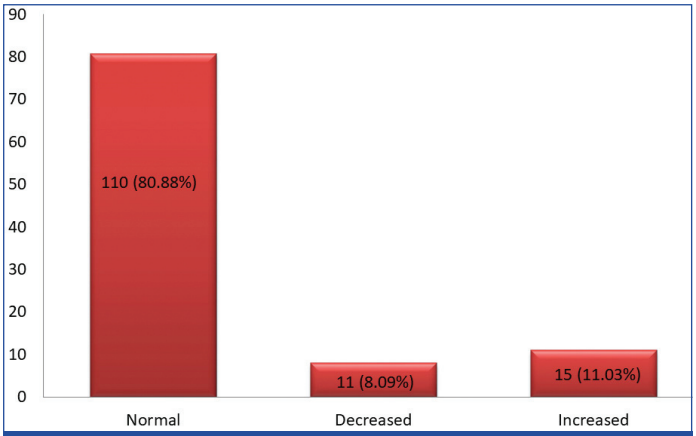


[Table/Fig-3]: Distribution of study subjects based on serum calcium level.

Parameters	Normal calcium (Mean±SD)	Decreased calcium (Mean±SD)	p-value
RBS (mg/dL)	167.65±110.98	191.78±113.47	0.239
Urea (mg/dL)	31.18±16.70	32.11±20.87	0.778
Creatinine (mg/dL)	0.93±0.51	0.98±0.61	0.653
Albumin (g/dL)	3.76±0.50	3.59±0.62	0.090
AST (U/L)	53.87±46.66	60.04±34.47	0.429
ALT (U/L)	50.90±55.02	52.52±36.03	0.857
ALP (U/L)	103.30±40.35	105.22±81.07	0.854
Serum uric acid (mg/dL)	4.24±1.61	3.93±1.67	0.290
CRP (mg/L)	8.24±3.44	8.89±4.13	0.328
LDH (IU/L)	350.20±166.56	351.44±155.94	0.966
D-dimer (ng/mL)	478.74±195.43	570.37±239.03	0.018*

[Table/Fig-4]: Comparison of the parameters between normal calcium (8.5-11 mg/dL, n=94) and decreased calcium (<8.5 mg/dL, n=42) groups.
RBS: Random Blood Sugar; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; ALP: Alkaline Phosphatase; CRP: C-Reactive Protein; LDH: Lactate Dehydrogenase; *p-value <0.05 was considered statistically significant (Student's t-test)

Study subjects were compared based on serum uric acid level as shown in [Table/Fig-5] majority 110 (80.88%) patients had normal serum uric acid level. However, 11 (8.09%) had decreased and 15 (11.03%) had increased serum uric acid level.



[Table/Fig-5]: Distribution of study subject based on serum uric acid level.

The mean value of RBS was significantly higher among patients with increased serum uric acid. Further, mean value of urea and creatinine was higher among patients with increased uric acid as compared to patients with normal and decreased level of uric acid and it was found to be significant. Similarly, mean value of serum calcium and LDH was significantly higher among patients with increased uric acid [Table/Fig-6].

Parameters	Normal uric acid (Mean±SD)	Decreased uric acid (Mean±SD)	Increased uric acid (Mean±SD)	p-value
RBS (mg/dL)	184±109.60	127.93±56.06	240.36±154.16	0.026*
Urea (mg/dL)	29.43±15.22	23.93±11.12	55.36±26.14	0.000*
Creatinine (mg/dL)	0.91±0.42	0.67±0.49	1.57±0.94	0.000*
Albumin (g/dL)	3.68±0.56	3.73±0.46	3.79±0.58	0.778
AST (U/L)	55.68±44.33	49.07±23.68	65.43±48.24	0.588
ALT (U/L)	52.29±54.14	44.13±22.94	52.86±26.21	0.832
ALP (U/L)	106.32±60.60	81.40±33.89	110±45.32	0.264
Serum calcium (mg/dL)	8.87±0.91	8.25±0.92	9.10±1.04	0.028*
CRP (mg/L)	8.13±3.48	9.59±4.05	9.73±4.52	0.141
LDH (IU/L)	364±173.4	333.76±144.78	469.07±203.90	0.010*
D-dimer (ng/mL)	492.13±214.43	573.73±205.83	575.71±215.46	0.186

[Table/Fig-6]: Comparison of the parameters between normal uric acid (2.5-6 mg/dL, n=110), decreased uric acid (<2.4 mg/dL, n=11) and increased serum uric acid (>6 mg/dL, n=15) groups.
RBS: Random blood sugar; AST: Aspartate amino transferase; ALT: Alanine amino transferase; ALP: Alkaline phosphatase; CRP: C-reactive protein; LDH: Lactate dehydrogenase; ANOVA test was used for analysis, *p-value <0.05 was considered statistically significant

Among 110 survived COVID-19 patients majority 83 (75.45%) had normal serum calcium level. Similarly, 91 (82.73%) had normal serum uric acid level, as compared to 9 (8.18%) of decreased and 10 (9.09%) of increased serum uric acid level [Table/Fig-7].

Survived (110)	Serum calcium		Serum uric acid		
	Normal (8.5-11 mg/dL)	Decreased (<8.5 mg/dL)	Normal (2.5-6 mg/dL)	Decreased (<2.4 mg/dL)	Increased (>6 mg/dL)
Number (%)	83 (75.45%)	27 (24.55%)	91 (82.73%)	09 (8.18%)	10 (9.09%)
Mean±SD	9.31±0.53	7.91±0.66	3.85±0.9	2.02±0.25	7.8±0.9

[Table/Fig-7]: Comparison of different values of serum calcium & serum uric acid among survived COVID-19 patients.

Out of 26 non survived COVID-19 patients 15 (57.69%) had decreased serum calcium level. However majority of non survived patients had normal serum uric acid level, only 5 (19.23%) patients had increased uric acid and 2 (7.69%) patients were having low serum uric acid level [Table/Fig-8].

Non survived (26)	Serum calcium		Serum uric acid		
	Normal (8.5-11 mg/dL)	Decreased (<8.5 mg/dL)	Normal (2.5-6 mg/dL)	Decreased (<2.4 mg/dL)	Increased (>6 mg/dL)
Number (%)	11 (42.31%)	15 (57.69%)	19 (73.08%)	02 (7.69%)	05 (19.23%)
Mean±SD	9.31±0.64	7.51±0.87	3.75±0.79	2.2±0.28	7.48±1.27

[Table/Fig-8]: Comparison of different values of serum calcium and serum uric acid among non survived COVID-19 patients.

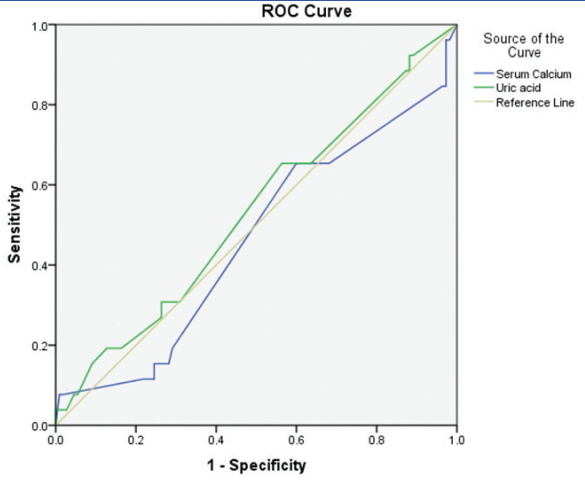
A significant positive correlation was found between serum uric acid levels with LDH (r-value=0.231; p-value=0.007). Whereas, Serum calcium showed negative correlation with CRP (r-value=-0.55; p-value=0.526) and D-dimer (r-value=-0.052; p-value=0.551) but it was not found statistically significant [Table/Fig-9].

Parameters	C-reactive protein		Lactate dehydrogenase		D-dimer	
	r-value	p-value	r-value	p-value	r-value	p-value
Serum calcium	-0.55	0.526	0.074	0.390	-0.052	0.551
Serum uric acid	0.081	0.346	0.231	0.007*	0.077	0.374

[Table/Fig-9]: Correlation between serum calcium, serum uric acid with inflammatory markers.
Pearson's correlation test used for analysis

The ROC analysis was done to predict the prognostic performance of serum calcium and uric acid to predict the development of poor outcome [Table/Fig-10]. It found that, the Area Under the Curve (AUC) for serum uric acid (0.530) was higher as compared to serum calcium (0.460). Therefore serum uric acid with higher AUC emerged

as a better biomarker towards the prediction of poor outcome with COVID-19 infection.



Test result variable (s)	Area Under the Curve (AUC)
Serum calcium	0.460
Uric acid	0.530

[Table/Fig-10]: ROC curve for prognostic performance of serum calcium and serum uric acid to predict the outcome.
AUC for serum calcium and serum uric acid

DISCUSSION

In the present clinical retrospective study, the correlations between serum calcium and serum uric acid with outcome of COVID-19 infection was investigated. Out of 136 study participants, the incidence of hypocalcaemia was seen in 42 (30.88%) cases and hyperuricaemia was in 15 (11.03%) cases. Decreased serum calcium was observed significantly higher among non survived COVID-19 patients.

In the present study, it was observed that hyperglycaemia, hypoalbuminaemia and increased inflammatory mediator like CRP, LDH and D-dimer concentrations among non survival group COVID-19 as compared to survival of COVID-19 patients indicating higher inflammation and tissue damage among the former ones. These findings were in accordance with previously published article by Huang C et al., they reported that the median value of AST 44 U/L), ALT (49 U/L), LDH (400 U/L) and D-dimer (2.4 mg/L) were higher among patients admitted in Intensive Care Unit (ICU) as compared to non ICU patients (34 U/L, 27 U/L, 281 U/L and 0.5 mg/L, respectively) whereas median value of serum albumin level (2.79 g/L) was decreased among patients admitted in ICU [2]. Elevated serum CRP and D-dimer signifies inflammatory response and coagulation disorder, further elevation of LDH detonates the tissue damage induced by COVID-19 infection [9,19]. Studies have shown significant association between hypocalcaemia and inflammatory markers that reflect severity of the disease. Present study showed a negative association of calcium levels with CRP levels and D-dimer. This is similar to the study done by Sun JK et al., [20].

In a study conducted by Liu J et al., they found that 62.6% had hypocalcaemia and patients with hypocalcaemia were presented with poor outcome (47.8% (32/67) vs 25% (10/40), p-value=0.02). In the present study it was found that among non survived COVID-19, 57.69% had decreased serum calcium level and 42.31% had normal serum calcium level [9].

Uric acid is the end product of purine metabolism and it is a potent antioxidant that alarms and initiates immune system in response to cell injury/death and thus clears the dead cells/tissues. During the process of tissue damage, intracellular uric acid is released resulting in hyperuricaemic state. A study by Schuler CF et al., showed that invasion of virus to the respiratory system could induce hyperuricsemia [18].

In the present study, it was observed elevated uric acid levels among non survived COVID-19 patients. Further, there were significant increased levels of blood sugar, urea, creatinine, calcium and LDH among the patients with hyperuricaemia. Similar to the study by Zeng T et al., a positive correlation was found between uric acid and inflammatory markers (CRP, LDH and D-dimer) in patients with COVID-19 [19].

In the present study it was found that majority of non survived (73.08%) had normal serum uric acid level however, 19.23% patients had increased uric acid as compared to 7.69% patients who had low serum uric acid level. Present study results are in concurrence with the study done by Zheng T et al., they concluded that there was a significant differences in the rates of hyperuricaemia (OR: 3.17, 95% CI: 2.13-4.70; p-value <0.001) between deceased and recovered patients [19].

In the present study, ROC analysis was done to predict the prognostic performance of serum calcium and uric acid to predict the development of poor outcome. It was found that AUC for serum uric acid level (0.530) was more compared to serum calcium (0.460). In the present study serum uric acid emerged as a better biomarker towards the prediction of prognosis of patients with COVID-19 infection. Thus, initiation of therapy based on the alterations in serum calcium and serum uric acid level will be beneficial in lessening the burden of mortality due COVID-19 infection and increases the survival rate.

The results of the present study provided the information regarding the effect of serum calcium and serum uric acid level on outcome of COVID -19 infections and survival rate. Hence, further studies are required to know the effect of calcium supplementation in treating hypocalcaemia and prognosis of COVID-19 infected patients and to know the specific relationship between admission serum uric acid lowering drug and its outcomes in hospitalised patients.

Limitation(s)

One of the potential limitations of the present study is small sample size. Secondly, referred cases with corrected/initiation of treatment for altered serum calcium and serum uric acid levels were not considered.

CONCLUSION(S)

Present study has shown that serum calcium levels were lower and serum uric acid levels were elevated among non survived patients. Further, serum uric acid emerged as a better biomarker towards the prediction of prognosis of patients with COVID-19 infection. Findings of the present study can speculate that low calcium and elevated serum uric acid levels in COVID-19 patients could be due to viral associated cytokine and increased immune response to the damaged tissues, respectively. Therefore, early evaluation of serum calcium levels and serum uric acids could aid in predicting the outcome of the disease and helps to circumvent the damage of multiple organs.

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