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Evaluation of Pattern and Impact of Electrolytes Abnormalities in Critically Ill Covid-19 Patients

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ABSTRACT

OBJECTIVE: To evaluate the pattern of serum electrolytes abnormalities and their impact on ICU admitted Covid-19 patient outcomes.

METHODOLOGY: This retrospective study was carried out at OMI hospital and Dr. Ziauddin Hospital, Karachi, Pakistan, between August to December 2020. Total 102 PCR positive, ICU admitted with severe Covid-19 patients as per WHO criteria were included. The patient's demographic characteristics, clinical features including co-morbidities, electrolytes reports at the time of admission, length of ICU and/or hospital stay, and outcome (expired/survived) were evaluated.

RESULTS: Biochemical testing found abnormal electrolyte levels in 90.2% ICU admitted Covid-19 patients. Electrolytes abnormalities including hyponatremia 45.1%, hypermagnesemia 40.2%, hypocalcemia 31.4%, hyperchloremia23.5% and hyperphosphatemia in 20.6% patients. Out of the total, 28.4% of patients needed invasive respiratory support, and 37.3% of patients could not survive. A higher incidence of mortality (39.1% vs. 20%) was seen in patients with electrolytes abnormalities as compared to the patients presented with normal values.

CONCLUSION: Electrolyte abnormalities were found in 90% of the ICU Admitted Covid-19 patients. The most common abnormalities found among the patients were hyponatremia, hypermagnesemia, and hypocalcemia. The findings revealed that several electrolytes imbalances appear to harm patients' in-hospital outcomes. Electrolyte assessment of Covid-19 patients at the time of admission would be helpful in risk stratification for adverse outcomes.

KEYWORDS: Covid-19, critically ill, ICU stay, serum electrolytes, abnormalities, respiratory support, death.

INTRODUCTION

Within a few months of the World Health Organization(WHO) announcing a global pandemic, several million cases of coronavirus disease (Covid-19) have been reported globally since December 2019[1]. Different updates on the clinical characteristics of infected patients have been unveiled since Covid-19, an infectious disease caused by extreme acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China[2]. With multisystem involvement, Covid-19 is a potentially fatal disease. The human respiratory system, however its primary target. This triggers severe pneumonia and develops acute respiratory distress syndrome (ARDS) in the respiratory system. In addition, the condition can affect multiple organs system of the human body including the neurological, renal, gastrointestinal and coagulation systems[3]. An increase in morbidity and mortality among critically ill patients is associated with electrolyte imbalances (sodium, calcium, potassium, chloride, phosphate, and magnesium)[4].

Electrolyte imbalances in patients were stated in several recently conducted studies. Electrolyte imbalances have resulted in contributing to cardiovascular and renal diseases, increased hospitalization time, and mortality caused by SARS-CoV-2 infection[5,6]. Some data has been presented in early Covid-19 studies that electrolyte abnormalities; sodium, calcium, potassium, and chloride, can also be found upon patient presentation[6-8].

By binding Angiotensin-converting enzyme 2(ACE2) to the cell membrane, human cells invade by SARS-CoV-2. In several human tissues where ACE2 is widely distributed, eg: lungs, heart, liver, and kidney, organ dysfunction is seen. For the renin-angiotensin system (RAS) main axis, ACE2 is used as the primary counter-regulatory pathway, which plays important role in regulating blood pressure and electrolytes. This virus binds to ACE2 and increases ACE2 degradation, thus reducing the RAS counteract of ACE2. The end result is the rise of serum sodium level and water re-absorption, subsequently high blood pressure and potassium (K+) excretion. In addition, Covid-19 patients may also have GI symptoms, such as vomiting and diarrhea. The effects of Covid-19 on RAS and the gastrointestinal system are likely to lead to disturbances of electrolyte homeostasis and pH[2,9]. Previous studies also indicated such imbalances of serum electrolyte and glucose levels in Covid-19 individuals[6,10,11].

There is an association between hyponatremia and atypical pneumonia, which leads to ICU admission, longer duration of stay, higher hospital costs, and high incidence of mortality[2]. **Duan J et al** reported transition of the Covid-19 to severe stage these markers, levels of sodium, potassium, and chloride had high predictive capacity [12]. Low baseline sodium, chloride, and calcium levels were found by **Tezcan ME et al** to be correlated with higher mortality rates, increased Intensive care unit stay and mechanical ventilator requirements, and prolonged hospital stay. The predominant electrolyte abnormality associated with adverse findings is hyponatraemia[2,3]. Low sodium, potassium, and calcium serum concentrations are directly associated with the severity of the disease. Though it is not yet clear if there is a risk of Covid-19-related hyponatremia, hypocalcemia, or hypocalcemia, more clinical knowledge will be required to interpret these abnormalities. These conditions, in particular hypokalemia, may have considerable consequences for the treatment of patients and may theoretically lead to the unraveling of the fundamental pathogenic pathways of Covid-19. Acute respiratory distress syndrome (ARDS) and acute cardiac injury, which are frequent complications of covid-19, are known to intensify hypokalemia, especially in patients with underlying lung or heart disease[6,13,14].

Poor prognosis and severe disease have been related to a low level of potassium at enrollment, but little is understood about the dynamics over time. In previous research, chloride homeostasis has been briefly addressed without obtaining any prognostic benefit at admission. The prevalence of electrolyte abnormalities is significantly higher among severely ill Covid-19 patients. Serum sodium (Na+) level in 57-77.1%, potassium (K+) level in 50%, calcium (Ca2+) level in 28.6%, magnesium(Mg) level in 15.7% patients were found to be low and high magnesium level was found in 7.14% Covid-19 patients[2,6,15,16].

Our research aims to describe the dynamics of serum electrolytes at presentation, and the outcomes of patients with Covid-19 who are critically ill. This study is intended to help ICU health providers optimize Covid-19 patients' electrolyte management. At present, there is limited evidence about severe Covid-19 patients. Therefore, knowledge of these corona virus-induced metabolic abnormalities will play a role in disease prognosis initial therapeutic measures, and disease surveillance. Knowledge and understanding of the possible pathophysiological pathways of Covid-19 could provide an opportunity to develop a new therapeutic strategy. Therefore, we tried to strengthen our present understanding of electrolyte imbalance in ICU admitted Covid-19 patients. The current study with structured measurements of serum levels with clinical evaluation of electrolytes input and output will add great value to the existing literature and will also provide crucial information for decision making in the current public health crisis.

METHODOLOGY

This retrospective study was conducted at OMI hospital and Dr. Ziauddin Hospital, Karachi, after taking ethical approval. The sample size was calculated by using the online sample size calculator Open Epi. Taking statistics of hypomagnesemia 7.14% in Covid-19 patients admitted in ICU[2], at the margin of error 5% and confidence interval 95%. Data of 102 Covid-19 patients was obtained by using the "Non-probability consecutive sampling technique" from hospitals' medical records. Only those Covid-19 adult (>18 years age) patients irrespective of gender who were treated at the intensive care unit (ICU) from August to December 2020 were included.

Covid-19 or SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (PCR) assay of nasal and pharyngeal swabs and following WHO[17] criteria for only severe (signs of pneumonia with respiratory rate $\geq$ 30 breaths/min or SpO2 < 90% on room air) and critical (development of Acute Respiratory Distress Syndrome, septic shock or multi-organ dysfunction) Severe Covid-19 patients admitted in ICU were enrolled in this study. Patients less than 18 years of age, who had other causes of electrolyte imbalances, chronic organ failure, immunodeficiency, and terminal cancer, were excluded.

Electrolytes levels were obtained from the laboratory database. The patient's electrolyte values i.e. serum sodium, potassium, chloride, magnesium, calcium, bicarbonate, phosphorus, and albumin at the time of admission were extracted from their medical records. According to the standard laboratory reference range, the values of these markers are further categorized as hypo and hyper.

Normal reference values of different electrolytes are as followed:135-145 mmol/L –Serum sodium level, 3.5-5 mmol/L-Potassium level, 95-105 mmol/L- Chloride level, 1.7-2.2 mg/dL-Magnesium level, 8.5-10.2 mg/dL – calcium level, 2.5 – 4.5 mg/L-phosphorus level. Demographic and clinical characteristics including age, gender, co-morbid status were also obtained from patients' medical records. Patient outcomes (Non-invasive/invasive reparatory support, duration of hospitalization, duration of ICU stay, and in-hospital mortality) and impact of the electrolyte abnormalities on outcomes were also evaluated in this study.

Data was entered and analyzed by using SPSS version 24. Descriptive statistics were calculated for study variables. Mean and standard deviation were computed for quantitative variables and frequency and percentages were calculated for qualitative variables. Associations between outcomes and confounders were observed by using the Chi-square/Fisher exact test. Comparisons of quantitative variables were done using an independent t-test. At P-value $\leq$0.05 as significant and power of the test kept 80%.

RESULTS

In this study, we included 102 critically ill Covid-19 patients admitted in ICUs at two different private hospitals in Karachi, Pakistan. In this cohort mean age of the patients was 63.2+/-13.2 years. 57.8% were over 60 years of age, 37.3% were between 41-60 years and remained below 40 and above 18. Male patients were 56.9%. Hypertension, diabetes mellitus, and IHD were most frequently found co-morbidities (**Table I**). Electrolyte levels at the time of admission were assessed and found abnormal in 90.2% Covid-19 patients. Where only 1 abnormal level was found in 22(21.6%), 2 in 30(29.4%), 3 in 20(19.6%), 4 in 16(15.7%), 5 in 3(2.9%) and 6 abnormal electrolytes found in 1(1%) patients. Approximately 70% of patients had more than one electrolyte imbalance. 64.7% patients had hyponatremia, 40.2% hypermagnesemia, 36.3%, hypocalcemia, 31.4%, 23.5% hyperchloremia, and 20.6% were found to have hyperphosphatemia. The most common abnormalities found in our study were hyponatremia, hypermagnesemia, and hypocalcemia, while less frequent abnormalities were hypokalemia, hyperkalemia, hypochloremia, hypomagnesemia, and hypophosphatemia. (**Figure I**) 71.6% of patients required non-invasive respiratory support and the remaining 28.4% needed invasive mechanical ventilators. The mean ICU stay of Covid-19 patients was 7.4+/-5.8 days while overall hospital stay was 10.1+/-6.4 days. Furthermore, 37.3% of patients died. (**Table I**)

Comparison of overall electrolyte abnormalities with demographic, clinical profile, and outcome of the patients was done. Most of the factors had no statistical difference (P-value > 0.05), while gender and outcome respiratory support had a significant association with electrolyte abnormality (P-value<0.05). (**Table I**)

A comparison of electrolyte abnormalities with the outcome of the patients was done. Although there was no statistical difference was found (P-value>0.05) the frequencies showed there is a high prevalence of electrolyte abnormalities in patients who died. Patients who died, among them 31.6% had hypocalcemia, 44.7% had hyponatremia. Respiratory support showed a significant association with patient outcomes. Out of all patients who needed invasive mechanical ventilation only 20.3% survived. On the other hand, 79.7% of those who were on noninvasive ventilation could survive. ICU and hospital stay was relatively higher in patients who had electrolyte abnormalities as well as who died in comparison to the patients who survived. While there was no difference observed in-hospital stay among patients who died or survived.

A comparison of electrolyte abnormalities with respiratory support received by the patients was done. As similar to the previous finding there was no statistical difference was found here as well (P-value > 0.05) but the frequencies showed there is a relatively high prevalence of electrolyte abnormalities in patients who were on invasive support. Among those who were on invasive support 58.6% had hyponatremia, 48.3% had hypermagnesemia and 37.9 had hypocalcemia. ICU and hospital stay was higher in patients who were on invasive respiratory support as compared to the patients who were on non-invasive support. (**Table II**)

In this study, we also explored the association between patient outcomes and demographic/ medical profile. Age showed a significant effect on mortality in these patients. The mortality rate was higher in older age patients (P-value: 0.009). There was a slightly higher incidence of mortality among males when compared to females. Mortality was seen more among patients have with co-morbidities especially patients with hypertension, DM, and IHD. Comparison of electrolytes levels between expired and survived patients was also stated. (**Table III**)

TABLE I: DISTRIBUTION AND COMPARISON OF DEMOGRAPHIC, DISEASE-RELATED PROFILE AND OUTCOMES OF THE COVID-19 PATIENTS

Associated factors		Electrolytes Abnormalities		Total	P-values
		Yes	No		
Age groups	>40 years	5(5.4%)	0(0%)	5(4.9%)	0.260**
	41-60 years	32(34.8%)	6(60%)	38(37.3%)	
	>60 years	55(59.8%)	4(40%)	59(57.8%)	
	Mean+/-SD			63.2+/-13.2	
Gender	Male	49(53.3%)	9(90%)	58(56.9%)	0.026*
	Female	43(46.7%)	1(10%)	44(43.1%)	
Co-morbidities	Diabetes mellitus	54(58.7%)	3(30%)	57(55.9%)	0.083**
	Hypertension	54(58.7%)	4(40%)	58(56.9%)	0.257**
	Asthma	4(4.3%)	1(10%)	5(4.9%)	0.432**
	COPD	4(4.3%)	0(0%)	4(3.9%)	0.501**
	IHD	25(27.2%)	3(30%)	28(27.5%)	0.849**
Respiratory support	Invasive	29(31.5%)	0(0%)	29(28.4%)	0.029*
	Non-invasive	63(68.5%)	10(100%)	73(71.6%)	
ICU stay		7.67+/-5.94	5.10+/-4.46	7.4+/-5.8	0.188**
Hospital stay		10.39+/-5.6	7.90+/-4.84	10.1+/-6.4	0.248**
Outcome	Expired	36(39.1%)	2(20%)	38(37.3%)	0.235**
	Survive	56(60.9%)	8(80%)	64(62.7%)	
Total		**92(90.2%)**	**10(9.8%)**	**102(100%)**	

FIGURE I: PATTERN OF ELECTROLYTES ABNORMALITIES

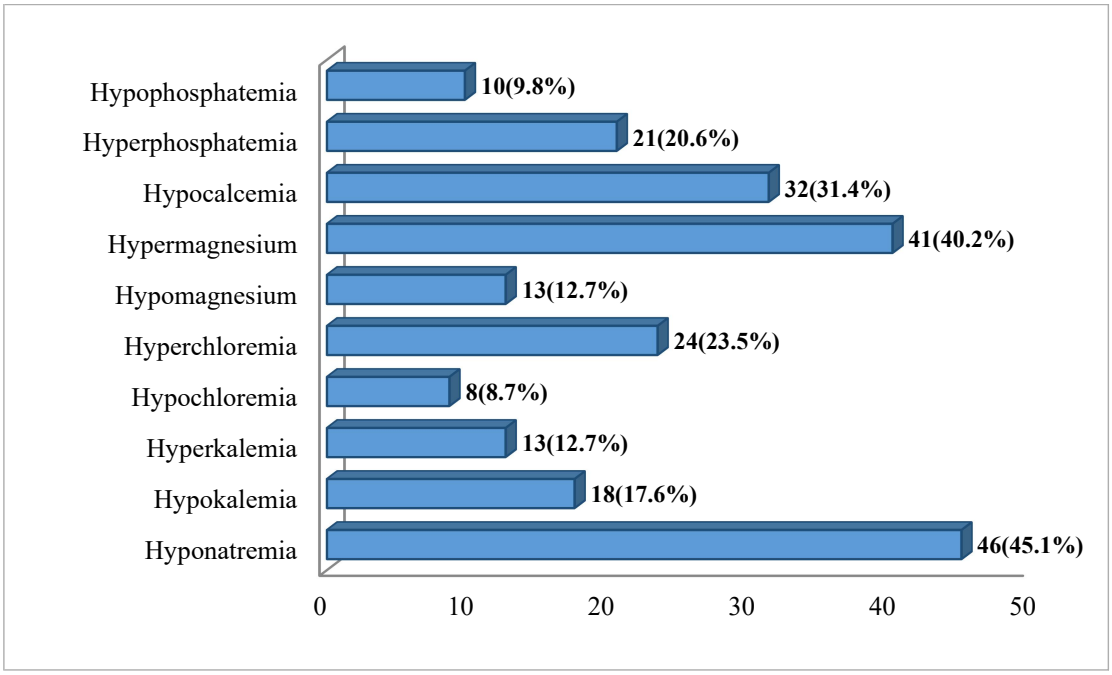

TABLE II: COMPARISON OF ELECTROLYTE ABNORMALITIES AND OUTCOMES IN COVID-19 PATIENTS

Electrolyte abnormalities	Respiratory distress		Sig.	Outcome		Sig.
	Non-invasive	Invasive		Expired	Survived	
Hyponatremia	29(39.7 %)	17(58.6%)	0.084	17(44.7%)	29(45.3%)	0.955
Hypokalemia	13(17.8%)	5(17.2%)	0.946	5(13.2%)	13(20.3%)	0.359
Hyperkalemia	9(12.3%)	4(13.8%)	0.537	6(15.8%)	7(10.9%)	0.545
Hyporchloremia	6(8.2%)	2(6.9%)	0.823	5(13.2%)	3(4.7%)	0.145
Hyperchloremia	18(24.7%)	6(20.7%)	0.670	11(28.9%)	13(20.3%)	0.320
Hypomagnesaemia	8(11%)	5(17.2%)	0.290	3(7.9%)	10(15.6%)	0.207
Hypermagnesaemia	27(37%)	14(48.3%)	0.294	18(47.4%)	23(35.9%)	0.255
Hypocalcaemia	21(28.8%)	11(37.9%)	0.368	12(31.6%)	20(31.2%)	0.972
Hyperphosphatemia	18(24.7%)	3(10.3%)	0.107	11(28.9%)	10(15.6%)	0.108
Hypophosphatemia	7(9.6%)	3(10.3%)	0.582	4(10.5%)	6(9.4%)	0.522
Outcomes						
ICU Stay	6.7+/-5.7	9.1+/-6.0	0.576	8.4+/-6.0	6.8+/-5.7	0.185
Hospital Stay	9.6+/-6.5	11.4+/-6.2	0.709	10+/-6.3	10.2+/-6.6	0.885

TABLE III: ASSOCIATION OF DEMOGRAPHIC AND MEDICAL PROFILE WITH OUTCOMES OF COVID-19 PATIENTS ADMITTED IN ICU.

Associated factors		Outcome		P-values
		Expired	Discharge	
Age groups (in years)	Less than 40	0(0%)	5(7.8%)	0.009 $^{\chi}$
	41-60	9(23.7%)	29(45.3%)	
	More than 60	29(76.3%)	30(46.9%)	
Gender	Female	16(42.1%)	28(43.8%)	0.871 $^{\chi}$
	Male	22(57.9%)	36(56.2%)	
Diabetes mellitus		23(60.5%)	34(53.1%)	0.467 $^{\chi}$
Hypertension		27(71.1%)	31(48.4%)	0.026 $^{\chi}$
Asthma		2(5.3%)	3(4.7%)	**0.896** $^{\chi}$
COPD		2(5.3%)	2(3.1%)	**0.591** ^{F}
IHD		18(47.4%)	10(15.6%)	0.001 $^{\chi}$
Comparisons of Electrolyte levels				
Sodium		134.8±5.96	134.9±5.64	0.916 $^{\tau}$
Potassium		4.26±0.74	4.08±0.69	0.223 $^{\tau}$
Chloride		101.66±6.93	102.05±6.31	0.773 $^{\tau}$
Magnesium		2.18±0.43	2.07±0.42	0.190 $^{\tau}$
Calcium		8.21±0.70	8.30±0.71	0.551 $^{\tau}$
Phosphorus		4.37±2.78	3.83±1.95	0.256 $^{\tau}$

Chi-square test= χ; Fisher exact test=F; Independent t-test=τ; significance level<0.05.

DISCUSSION

The present study aimed to report the pattern of electrolytes abnormalities. Further to evaluate the impact of these abnormalities in terms of in-hospital outcomes on ICU admitted COVID-19 patients. There is a need to study electrolytes imbalances and their management in a current pandemic. So far a few studies have been reported electrolyte abnormalities in COVID-19 patients. Studies conducted by **Sultana R et al**[2], **Sarvazadet al**[5], and **Tezcan ME et al**[3] assessed electrolyte imbalances in patients with COVID-19. These studies revealed that COVID-19 is strongly associated with low levels of sodium, potassium, calcium, magnesium, etc. From these studies, it was discovered that 38 to 77% [2,3,5] patients experienced hyponatremia, 7% to 50% [2,3,5] experienced hypokalemia, 9% to 28%[2,3] experienced hypocalcemia and15% to 32% [2,5] experienced hypomagnesemia. These results are comparable with our study findings as well as some other studies[6,11]. Previous studies were limited to sodium and potassium levels. Interestingly, we have reported electrolytes abnormalities in patients admitted in ICU with severe Covid-19 also evaluated the impact of these abnormalities on patient's in-hospital outcomes as well as reported parameters which previously neglected such as hypermagnesemia which makes our study unique and novel.

The findings of our study showed that males had a greater proportion in the cases with COVID-19 as compared to females. The results are in concurrence with the investigations performed in neighboring countries i.e. Chinese and Bangladeshi. Additionally, they also revealed a strong link between hypertension and diabetes with a higher rate of morbidity, severity, and poor prognosis in COVID patients[2,18,19]. With regards to high sodium levels, this study revealed that none of the patients had experienced hypernatremia which is in disagreement with previous studies[5,7,15]. The studies showed that high sodium levels led to a longer period of intensive care and had a high risk of mortality. With regards to low levels of sodium, 45.1% of patients had experienced hyponatremia in the present study cohort. The other two studies had reported similar findings for low sodium and severity of COVID-19[6,20]. Considering potassium levels, a study showed that hypokalemia also is a challenging condition to manage because of the deprivation of angiotensin-converting enzyme.[21]The pathophysiology of SARS-CoV-2 reflects upon the fact that decreased angiotensin-2 increases faecal potassium levels leading to hypokalemia.[5] In our study, only 17.6% of patients with severe COVID-19 experienced hypokalemia. Whereas **Chen D et al.**[11] revealed a higher frequency of hypokalemia in these patients. Therefore, it is advised that continuous monitoring and substitution of potassium levels might help reduce the risk of imbalance in electrolytes and their related complications.

Magnesium blocks calcium induction into immune-competent cells. Therefore; it is known as a calcium channel blocker. It inhibits systemic inflammation by inhibiting the production of cytokines and interleukins. Hence, hypomagnesemia exacerbates inflammation in COVID-19.[5]

Iotti et al[22] discovered stress as one of the causes of hypomagnesemia in a current pandemic. As with stress, catecholamines and corticosteroids push magnesium to extracellular space leading to an increase in faecal magnesium. In this study, 12.7% of patients experienced hypomagnesemia, and 40.2% of patients experienced hypermagnesemia. Duan J et al establish that potassium, sodium, and chloride levels can be used as predictors for severe COVID-19 disease[12].

The prognosis factors such as hospitalization and ICU admissions were also investigated in previous studies. It was revealed that high CRP levels, old age, and low white blood cells were associated with hospitalization[23] whereas prolonged hospitalization was linked with high ferritin levels and LDH[24]. Moreover, a systematic review found that hyponatremia and hypokalemia are

related to severe COVID[6] whereas high sodium, chloride, and potassium were linked to progression towards severe COVID.[12] In our study, it was found that low baseline sodium, chloride, and calcium levels were the significant predictors of higher incidence of mortality, higher ICU admission, prolonged stay and Mechanical ventilation requirement, and longer hospital stays. The aforementioned studies showed electrolyte abnormality has a strong association with severe COVID-19 and poor prognosis. However more commonly sodium levels are found low in the studies described above. Hence, targeting and monitoring sodium levels could help in better clinical outcomes for the patients as well as less challenging for physicians. Additionally, it is also important to assess other electrolyte abnormalities that have an impact on clinical outcomes such as hypocalcemia, hypermagnesemia, and hyperchloremia. The present study emphasizes the monitoring of these electrolytes for better treatment outcomes and preventing complication of the disease.

The current study has a limited sample size. Based on the findings of this research it is recommended to explore in-depth information on larger sample size for the longer follow-up to achieve generalizability. Moreover, causes and impact of electrolytes abnormality should be established and a wide variety of electrolytes should be assessed for a better prognosis of critically ill Covid-19 patients.

CONCLUSION

The study showed that most patients with severe Covid-19 had electrolyte abnormalities at the time of admission into the intensive care unit. Abnormalities were found in 90% of the ICU admitted Covid-19 patients while 70% of them had more than two electrolytes imbalances. Hyponatremia, hypermagnesemia, and Hypocalcemia were the most common electrolytic abnormalities encountered in this study. The electrolyte imbalances are strongly linked with poor clinical outcomes and factors such as the requirement of life support, prolonged ICU stays, and increase risk of mortality.

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AUTHOR CONTRIBUTIONS

All authors have contributed equally: Haroon A, Abbas SA, Khan A, Ali M, Qazi R, Kumar A.
A. Substantial contribution to conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
B. Drafting of the work or revising it critically for important intellectual content
C. Final approval of the version to be published
D. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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