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Review Article **Open Access**

Prognostic implication of hypocalcaemia in COVID-19: a systematic review

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Abstract:

Coronavirus disease-2019 (COVID-19) has been declared as a pandemic affecting several millions of people worldwide. It has varied clinical manifestations ranging from asymptomatic to critical illness. It has led to the mortality of several affected individuals. However, the prognosis seems to vary from one person to the other and efforts are being made to identify the prognostic factors. Hypocalcaemia has been identified as a poor prognostic factor with a high frequency among individuals affected with COVID-19. This review aims to estimate the prevalence of hypocalcaemia among COVID-19 patients and identify the poor prognostic factors associated with the presence of hypocalcaemia in COVID-19 patients. Electronic medical databases were searched for publications on the prognostic implications of hypocalcaemia in COVID-19 infection, and relevant articles were selected for systematic review following PRISMA algorithm. The prevalence of hypocalcaemia among patients with COVID-19 was 40.0-74.4%. There was a significant association between the rate of hospital admission, intensive care unit (ICU) admission as well as septic shock and hypocalcaemia in patients with COVID-19. Hypocalcaemia is also associated with a higher mortality rate in these patients. COVID-19 patients with hypocalcaemia tend to have elevated C-reactive protein, interleukin-6, alanine transaminase, procalcitonin, serum creatinine and low albumin. Hypocalcaemia is common in COVID-19 patients and is a poor prognostic factor in these patients. Presence of hypocalcaemia is associated with a severe illness and even death.

Keywords: COVID-19; hypocalcaemia; prognosis; systematic review

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Implication pronostique de l'hypocalcémie dans COVID-19: une revue systématique

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Abstrait:

La maladie à coronavirus-2019 (COVID-19) a été déclarée pandémie affectant plusieurs millions de personnes dans le monde. Il a des manifestations cliniques variées allant de la maladie asymptomatique à la maladie grave. Cela a conduit à la mortalité de plusieurs personnes touchées. Cependant, le pronostic semble varier d'une personne à l'autre et des efforts sont faits pour identifier les facteurs pronostiques. L'hypocalcémie a été identifiée comme un facteur de mauvais pronostic avec une fréquence élevée chez les personnes atteintes de COVID-19. Cette revue vise à estimer la prévalence de l'hypocalcémie chez les patients COVID-19 et à identifier les facteurs de mauvais pronostic associés à la présence d'une hypocalcémie chez les patients COVID-19. Les bases de données médicales électroniques ont été recherchées pour des publications sur les implications pronostiques de l'hypocalcémie dans l'infection à COVID-19, et les articles pertinents ont été sélectionnés pour une revue systématique suivant l'algorithme PRISMA. La prévalence de l'hypocalcémie chez les patients atteints de COVID-19 était de 40,0 à 74,4%. Il y avait une association significative entre le taux d'hospitalisation, l'admission en unité de soins intensifs (USI) ainsi que le choc septique et l'hypocalcémie chez les patients atteints de COVID-19. L'hypocalcémie est également associée à un taux de mortalité plus élevé chez ces patients. Les patients atteints de COVID-19 souffrant d'hypocalcémie ont tendance à avoir une protéine C-réactive élevée, l'interleukine-6, l'alanine transaminase, la procalcitonine, la créatinine sérique et un faible taux d'albumine. L'hypocalcémie est fréquente chez les patients atteints de COVID-19 et constitue un facteur de mauvais pronostic chez ces patients. La présence d'une hypocalcémie est associée à une maladie grave et même à la mort.

Mots clés: COVID-19; hypocalcémie; pronostic; Revue systématique

Introduction:

Coronavirus disease-2019 (COVID-19) is an acute viral infection of public health importance caused by the severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) (1). The SARS CoV-2 emerged from Wuhan, the largest and capital city of Hubei Province in Central China (1). The first outbreak was reported as an unexplained pneumonia among persons connected to a seafood market in Wuhan (2). It later spread all over China and across the globe. Bats are believed to be the natural reservoir of the virus but some researchers tend to dispute this (3). Transmission is commonly from person to person via respiratory droplets which are released during coughing, sneezing, talking, laughing and singing. However, transmission through contaminated fomites and aerosol, in specific situations, have been documented (4). As at the 20th of November 2020, over 56 million individuals have been affected worldwide (5). The distribution of number of infected cases across continents, as at 20th November 2020, is shown in Fig 1.

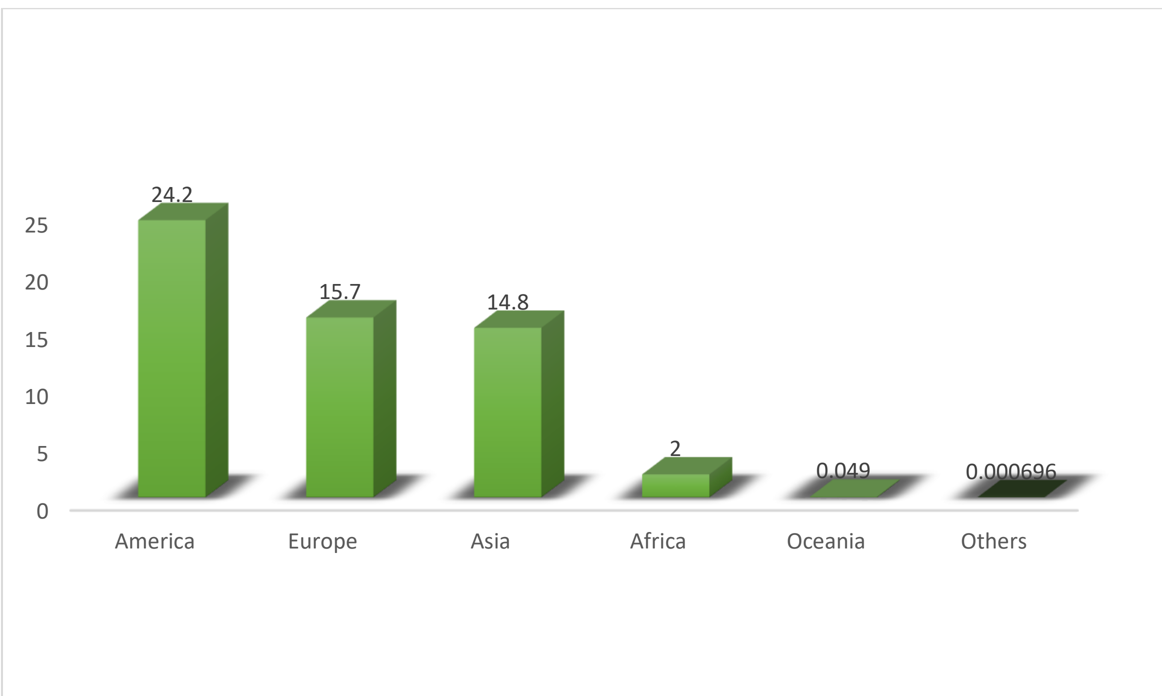

Fig 1: Distribution of COVID-19 cases across the continents of the world

The median incubation period of COVID-19 infection is about 5 days and by the 12th day, almost 100% of symptomatic infected individual would have started manifesting symptoms hence the adoption of 14 days to quarantine individuals who have been apparently exposed (6). A significant portion of the infected individuals are asymptomatic. Table 1 shows the percentages of asymptomatic cases reported from various studies, which range from 30.8-97.5%.

Table 1: Proportion of asymptomatic COVID-19 cases

Studies	Asymptomatic cases (%)
Nishiura et al., (7)	30.8
Lavezzo et al., (8)	41.0
Moriarty et al., (9)	46.5
Arons et al., (10)	52.2
Jung (11)	62.0
Ing et al., (12)	81.3
Baggett et al., (13)	87.8
Sutton et al., (14)	87.9
Lytras et al., (15)	97.5

In symptomatic cases, the most prominent symptoms are fever, cough and breathlessness (2). Others include fatigue, myalgia, headache, sore throat, abdominal pain and diarrhoea (16). Loss of taste, loss of smell, joint pain and chest pain have also been described (16,17). Essentially, differentiating COVID-19 from other causes of acute respiratory infection may be very difficult (18). Respiratory failure, sepsis, septic shock and multi-organ dysfunctions are some of the reported acute complications in those with progressive illness (19).

In diagnosing COVID-19, samples such as nasopharyngeal swab, oropharyngeal swab, tracheal aspirate and bronchoalveolar lavage are collected for reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which is the diagnostic procedure of choice for detection of SARS-COV-2 (19). However, naso and oropharyngeal swabs are the commonest specimens (19). Documented abnormalities in other laboratory test parameters are leukopenia or leukocytosis, thrombocytopenia, deranged electrolytes, urea creatinine as well as elevated D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH) and ferritin (20,21).

The commonest cause of death in COVID-19 patients is respiratory failure secondary to acute respiratory distress syndrome (22). The mortality pattern across the conti nents is shown in Fig 2 (5). The global case fatality rate, at the time of writing this manuscript, was 2.4% and the case fatality rates of different countries, ranging from 1.5-9.7%, are shown in Table 2 (23).

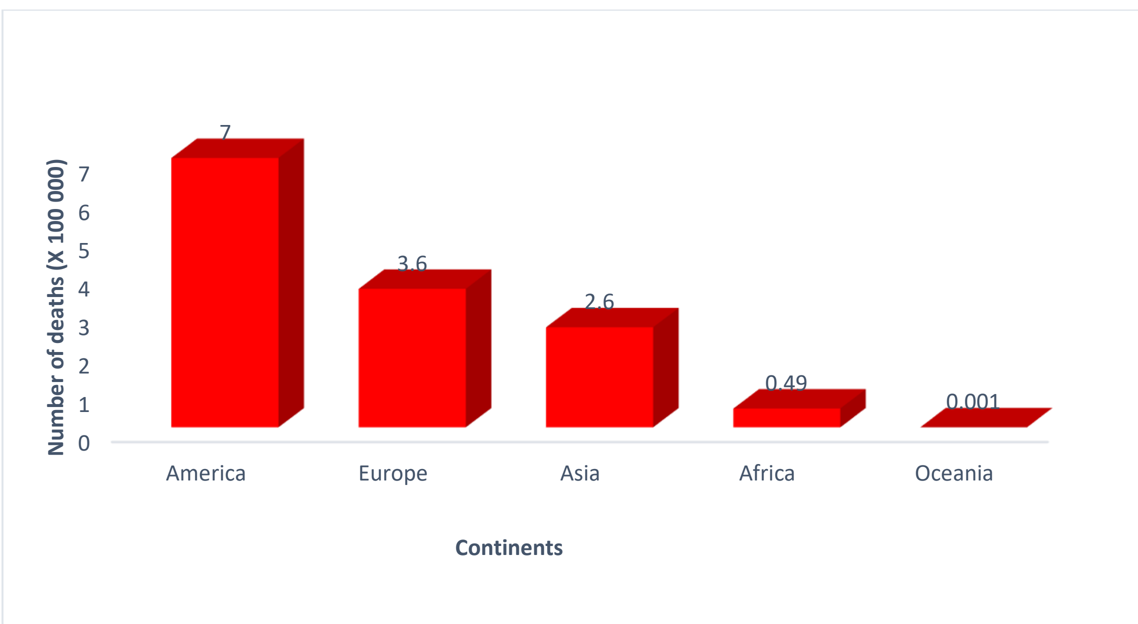

Fig 2: Distribution of COVID-19 deaths across continents

Table 2: Case fatality rates of COVID-19 in the 20 most affected countries in the world

No	Countries	Number of cases (Millions)	Case fatality rate (%)
1	USA	12.8	2.1
2	India	9.2	1.5
3	Brazil	6.1	2.8
4	France	2.1	2.3
5	Russia	2.1	1.7
6	Spain	1.6	2.7
7	UK	1.5	3.6
8	Italy	1.4	3.5
9	Argentina	1.4	2.7
10	Colombia	1.3	2.8
11	Mexico	1.0	9.7
12	Germany	0.95	1.5
13	Peru	0.95	3.7
14	Poland	0.91	1.6
15	Iran	0.88	5.2
16	South Africa	0.77	2.7
17	Ukraine	0.65	1.7
18	Belgium	0.60	2.8
19	Chile	0.54	2.8
20	Iraq	0.54	2.2

Several markers of poor prognosis in COVID-19 have been published. Old age and the male gender have been found to be associated with poor prognosis in COVID-19 patients (24). Smoking and co-morbidities such as hypertension, diabetes, chronic obstructive pulmonary disease and malignancy have been reported as prognostic factors (24). Examination findings of poor prognostic implication include tachypnoea, tachycardia, hypotension and reduced arterial saturation of oxygen using the pulse oximeter (24). Haematological parameters associated with poor prognosis are lymphopaenia, leukocytosis, neutrophilia and thrombocytopenia (24). Biochemical parameters that have been reported in COVID-19 patients with more severe illness include raised C-reactive protein, elevated D-dimer, lactate dehydrogenase, procalcitonin and raised cytokines such as interleukin-6 (24). Radiologically, consolidative or infiltrative changes as well as pleural effusion on chest imaging have also been reported to correlate with poor prognosis (24).

Calcium is required for the fusion of coronavirus to the human cells before they can gain entry into the cells (25). Generally, hypocalcaemia is not an uncommon finding in critically ill patients (26). Some of the possible explanations for this include vitamin D deficiency, reduced dietary intake and hypomagnesemia (27). Vitamin D deficiency has been documented to be highly prevalent in patients with COVID-19 (28). Studies have also shown that COVID-19 patients with hypocalcaemia also tend to have other poor prognostic factors such as lymphopenia, elevated D-dimer, raised C-reactive protein and increased alanine transaminase (ALT) (26). Patients with hypocalcaemia were found to have higher incidence of acute respiratory distress syndrome (ARDS) (26). Liu et al., (29) also found that hypocalcaemia is also associated with poor outcome in patients with COVID-19.

Some authors have reported that unsaturated fatty acids released during COVID-19 infection is responsible for the hypocalcaemia seen in patients with the illness, and the process is independent of the vitamin D status of patients (30). In support of this is the finding of Thomas et al., (42) who reported a high level of unsaturated fatty acids in patients with severe COVID-19 infection. This is a systematic review of studies reporting the prevalence and prognostic implications of hypocalcaemia in COVID-19 patients.

Methodology:

Electronic online accessible medical data bases were searched for studies on the prognostic implications of hypocalcaemia in COVID-19 infections. The online databases searched were Google Scholar, Public Library of Medicine (PubMed), African Journals Online (AJOL), Scopus and Web of Science. The terms searched were 'hypocalcaemia', 'prognostic factors', and 'COVID-19 infection'. Boolean operators such as 'AND' as well as 'OR' were used during the data search so as to improve the quantity and specificity of the articles retrieved. Grey literature was also searched. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram of the literature search and selection is shown in Fig 3.

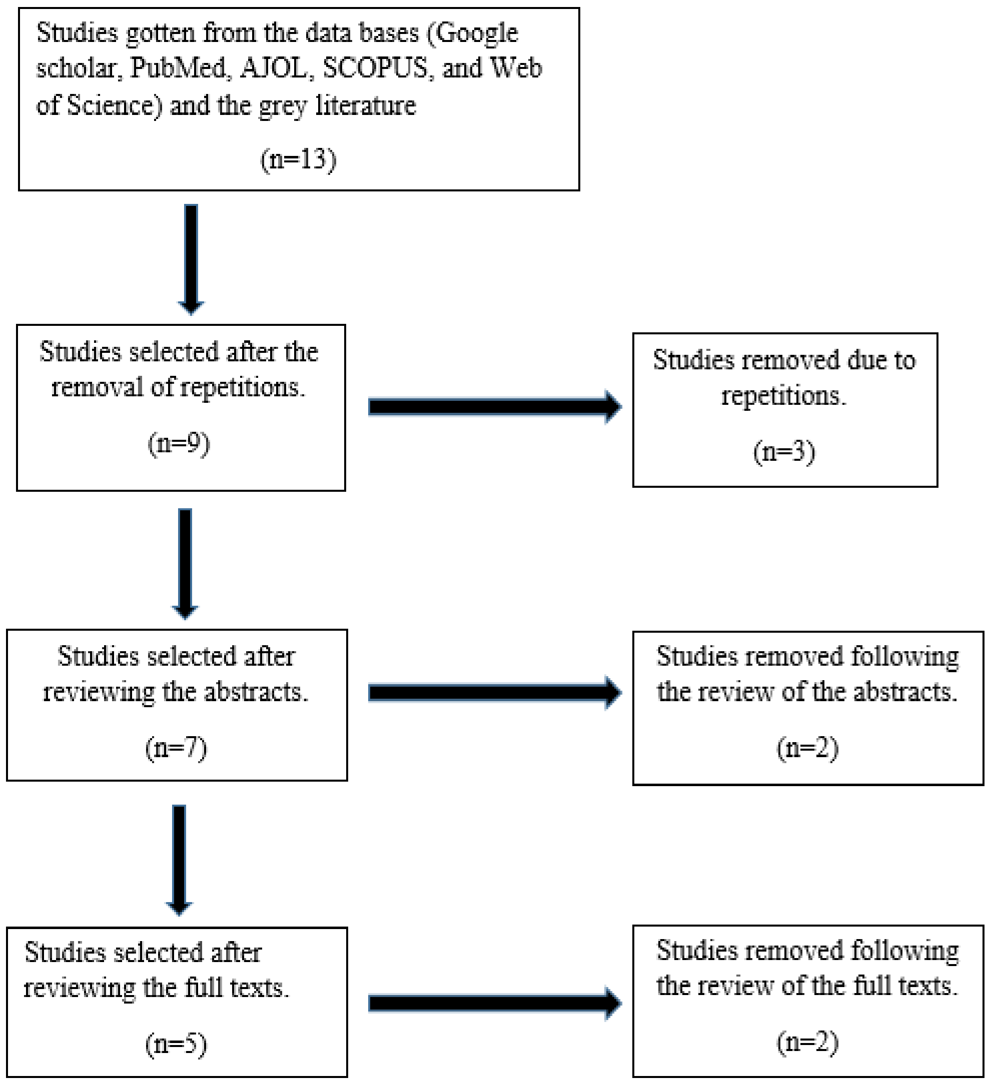

Fig 3: PRISMA flow diagram of the literature search and selection

The inclusion criteria were; studies done between 1st January, 2020 and 10th December, 2020 to determine the association between hypocalcaemia and poor prognostic factors in patients infected with COVID-19 done, and studies which abstracts and or full text were available at the searched databases or from the grey literature. The exclusion criteria included studies on COVID-19 not focused on the prognostic implications of hypocalcaemia, and studies which abstracts or main texts were not available for review. The databases were searched independently by the authors and the included studies were deemed appropriate by at least three of the five authors. Relevant data were extracted and presented in texts, tables and charts.

Results:

Table 3 shows the sample sizes in the selected studies, with a total sample size of 775 in the systematic review. The prevalence rates

Table 3: Sample sizes of the selected studies

Study	Sample size
Sun et al., (26)	241
Filipo et al., (31)	20
Liu et al., (29)	107
Torres et al., (32)	316
Raesi et al., (33)	91
Total	775

of hypocalcaemia among patients with COVID-19 patients in the various studies selected for this systematic review are shown in Table 4, which shows that the prevalence of hypocalcaemia among patients with COVID-19 was 40.0 -74.4%.

Table 4: Prevalence of hypocalcaemia among patients with COVID-19

Study	Prevalence rate (%)
Sun et al., (26)	74.4
Filipo et al., (31)	40.0
Liu et al., (29)	62.6
Torres et al., (32)	63.0
Raesi et al., (33)	59.3

Table 5 below shows the various poor prognostic factors associated with the presence of hypocalcaemia in COVID-19 patients across the selected studies. It shows the association between rate of hospital admission, intensive care unit (ICU) admission as well as septic shock with hypocalcaemia in patients with COVID-19. Hypocalcaemia is also associated with a higher mortality rate in patients with COVID-19 (26, 31,33).

Table 6 below shows laboratory parameters that are often deranged in hypocalcaemic COVID-19 patients (26,29,31-33). Commonly measured laboratory parameters such as the C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), albumin and others are statistically significantly associated with the presence of hypocalcaemia in patients with COVID-19 (26,29,31-33).

Among the selected studies, only the study by Sun et al., (26) measured the parathyroid hormone and vitamin D levels in a cohort of patients with COVID-19 even though all the selected patients did not have hypocalcaemia. Serum calcium was found to positively correlate with parathyroid hormone and negatively with vitamin D.

Table 5: Poor prognostic factors associated with hypocalcaemia among patients with COVID19

Prognostic factor	Sun et al., (26)	Filipo et al., (31)	Liu et al., (29)	Torres et al., (32)	Raesi et al., (33)
Septic shock	X				X
MODS	X				
ICU admission	X		X		X
ARDS	X				
Liver injury	X				
AKI	X				
Need for hospitalization	X	X	X		
Need for oxygen support	X	X	X	X	X
ICU admission		X	X	X	X

X=Presence; MODS=Multiple Organ Dysfunction Syndrome; ARDS=Acute Respiratory Distress Syndrome; AKI=Acute Kidney Injury; ICU=Intensive Care Unit

Table 6: Laboratory parameters often affected in hypocalcaemic COVID-19 patients

Laboratory parameters often elevated	Laboratory parameters often elevated
Erythrocyte sedimentation rate (ESR)	Lymphocyte
C-reactive protein (CRP)	Platelet
Lactate dehydrogenase (LDH)	Haemoglobin concentration
Alanine transaminase (ALT)	Albumin
Aspartate transaminase (AST)	Arterial partial pressure of oxygen (PaO_2)
D-dimer	
Procalcitonin	
Interleukin-6	
Total bilirubin	
Blood urea nitrogen (BUN)	
Creatinine	

Discussion:

In this systematic review, the prevalence rate of hypocalcaemia among patients with COVID-19 was high (40-74.4%). High prevalence rate of hypocalcaemia was also documented for severe acute respiratory syndrome (SARS) caused by the coronavirus, SARS-COV (34). Hypocalcaemia has also been found to be highly prevalent and is associated with poor prognosis in other viral infections such as measles and the viral haemorrhagic fever (35,36). Generally, hypocalcaemia has been extensively reported to be common among very ill patients and the causes are said to be multifactorial (37,38). The reported explanations for this observation include dysregulated secretion of parathyroid hormone, transient vitamin D deficiency, effects of catecholamines, multiple transfusion of citrated blood as well as the effects of certain drugs (38,39).

In a review by Mikhail et al., (40), the frequency of hypocalcaemia among patients with COVID-19 was reported to be 9.5-78%. In the general population, common causes of hypocalcaemia include chronic kidney disease, vitamin D deficiency, hypomagnesaemia, drugs and hypoparathyroidism (41). So far, the exact cause (s) of hypocalcaemia in COVID-19 patients is/ are not known (40). However, some plausible hypotheses have been proposed. One of the hypotheses was put forward by Singh et al., (30), who stated that COVID-19 is associated with the release of a large amount of free fatty acids into the circulation. It is believed that these free fatty acids bind to the circulating plasma calcium thereby rendering the patient hypocalcaemic. Thomas et al., (30) also corroborated this assertion by observing high levels of free fatty acids among patients with severe COVID-19 (42), a process said to be unrelated to the vitamin D status of the patient (30). Although vitamin D levels of hypocalcaemic patients in the selected studies for this systematic review were not determined, some other studies have documented the presence of vitamin D deficiency in patients with COVID-19 and this may account for the hypocalcaemia seen in these patients (28,43).

Hypocalcaemia has been extensively linked with the severity of COVID-19 infection (26,31-33). This systematic review demonstrates that hypocalcaemia is associated with septic shock in patients with COVID-19. The association between septic shock and hypocalcaemia is explained by certain observations such as, alteration in plasma pH which affects calcium ion binding to albumin, alteration of parathyroid hormone production by inflammatory mediators and deranged concentrations of plasma calcium binders namely, citrate, fatty acids and phosphate (44).

Acute respiratory distress syndrome (ARDS) is a common pathway leading to death in patients with severe COVID-19 and this systematic review clearly shows a significant association between hypocalcaemia and development of ARDS among COVID-19 patients (26). Even among patients without COVID-19, Thongprayoon et al., (45) observed that several case reports have documented a relationship between hypocalcaemia and ARDS. Some of the documented explanations for this observation include respiratory muscle weakness, laryngeal and bronchospasm and possibly tetany (45). Hypocalcaemia enhances contraction and tetany of airway smooth muscles by lowering the threshold for action potential (46). Also, hypocalcaemia has been reportedly linked with a high respiratory infection rate, higher inflammatory markers in the lungs and resultant progression of respiratory diseases (47).

This systematic review found an association between hypocalcaemia and acute kidney injury (AKI) as a marker of poor prognosis in patients with COVID-19. Hypocalcaemia was documented to be a poor prognostic index in patients with AKI secondary to COVID 19 infection (26). Hypocalcaemia has also been reported to be associated with the development of AKI in other critically ill patients without COVID-19 (48). Vitamin D deficiency has been documented in AKI and this has been put forward as one of the mechanisms by which AKI is associated with hypocalcaemia (49). Hyperphosphatemia, which is a common finding in AKI, is also a reported mechanism of hypocalcaemia in AKI (48). Furthermore, parathyroid hormone resistance in the bones has been documented in patients with AKI and this has been suggested as a possible mechanism of hypocalcaemia in AKI.

In this review, an association was found between hypocalcaemia and the risk of ICU admission. Hypocalcaemia has been extensively documented to affect different regulatory systems in the body (50). Hypocalcaemia is not an uncommon finding in critically ill patients (51). Hypocalcaemia has been reported to have a prognostic implication in critically ill individuals and is associated with increased mortality rate (52). This study also found a relationship with markers of inflammation such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin 6(IL-6), albumin and markers of specific organ dysfunction such as creatinine and alanine transaminase (ALT). The link between hypocalcaemia and inflammation has been attributed to vitamin D deficiency which is a common finding in inflammatory and infectious diseases as vitamin D has some anti-inflammatory properties (28,53,54).

This review has two limitations; (i) the number of studies that met the eligibility criteria was rather scanty, and (ii) most of the studies did not assay for vitamin D and parathyroid hormone levels which are important cofounders.

Conclusion:

In conclusion however, hypocalcaemia is common among patients infected with COVID-19 and is associated with the progression of the illness. The risk of mortality is higher in COVID-19 patients with hypocalcaemia. The presence of deranged levels of some biochemical parameters such as CRP, IL-6, serum creatinine and ALT is associated with low serum calcium levels. Therefore, hypocalcaemia is not only prevalent in COVID-19 patients but it is a marker of poor prognosis. In view of this, it is recommended to routinely measure serum calcium in patients with COVID-19.

Conflict of interest:

Authors declare no conflict of interest

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