

## Effects of COVID-19 Severity on Serum Calcium Levels

UMBREEN ASLAM<sup>1</sup>, MUHAMMAD KASHIF BASHIR<sup>2</sup>, NOSHEEN ZAFAR<sup>3</sup>, NIAMAT ALI<sup>4</sup>, SALMAN JAVED<sup>5</sup>, NAJAM-US-SEHAR SAEED<sup>6</sup>

<sup>1</sup>Assistant Professor Medicine, Sir Ganga Ram Hospital, Lahore

<sup>2</sup>Medical Officer, DHQ Hospital, Sheikhpura

<sup>3</sup>Senior Registrar Medical Unit 2, SHRH, FJMU

<sup>4</sup>Medical Officer, Services Hospital Lahore, Services Institute of Medical Sciences, Lahore

<sup>5</sup>Assistant Professor Gastroenterology, Services Institute of Medical Sciences, Lahore

<sup>6</sup>Assistant Professor Gastroenterology, Gujranwala Medical College, Gujranwala

Correspondence to: Umbreen Aslam, Email: [drumbreenaslam@gmail.com](mailto:drumbreenaslam@gmail.com), Cell: 03227932971

### ABSTRACT

**Background:** The hypocalcaemia may be a unique biochemical feature of COVID -19 that has the potential to influence disease severity and represents a new potential therapeutic target worth testing in this clinical setting. Because COVID -19 testing has primarily focused on individuals with respiratory symptoms rather than calcium levels, Therefore the objective of current study was to determine the effect of COVID-19 severity on Serum calcium levels.

**Methods:** After the ethical approval, all the RT-PCR positive patients from the record of corona isolation wards of Ganga Ram hospital Lahore. Demographic details including name, age, gender, complete history & examination serum Calcium level was noted recorded al from hospital files on a predesigned proforma. To assess clinical severity of coronavirus disease, all the enrolled patients' disease category as mild, moderate, severe & critical was note. Data was analyzed using SPSS-26. Association between age and gender between disease severity was determined by using Chi-square test. Binary logistic regression was applied to find out the effect of disease severity on serum calcium levels. P-value less than 0.05 were considered to be significant.

**Results:** 555 patients were enrolled in the current study. The mean ages of patients were 38.34+14.86. There were 300(54.1) male and 255(45.9) female, the severity of the disease shows that the majority 490(88.3%) of the patients had mild disease and 65(11.7%) had moderate disease. The mean serum calcium level was 8.7+0.34. The majority of patients had mild disease, of which 270 were female and 220 male and 230 among 31-50 years. The results of binary logistic regression show the effect of disease severity (Mild, Moderate) on calcium, age and gender. It was reported that only serum calcium, male gender and age category 30-50 years were a significant predictor of disease severity.

**Conclusion:** It was concluded from current study that majority of patients have mild disease severity and patients have normal serum calcium. The disease severity has no significant impact on the calcium levels as the majority of patient has mild disease.

**Keywords:** COVID-19, Disease Severity, Hypocalcemia

### INTRODUCTION

A novel coronavirus infection (COVID-19) outbreak has been reported in Wuhan, China, since late December 2019, affecting 215 countries.<sup>1</sup> The outbreak was linked to a seafood market in Wuhan, according to epidemiological investigations.<sup>2</sup> COVID -19 is a fast-onset infection but can be fatal, with a mortality rate of 2%. Severe disease onset can lead to death due to significant respiratory impairment and progressive respiratory failure.<sup>3</sup> While most coronavirus infections are insignificant, outbreaks of two beta coronaviruses, SARS-COV and MERS-COV, have resulted in more than 10,000 cases in the last two decades, with death rates of 10% at SARS-COV and 37% at MERS-COV.<sup>4</sup>

Acute respiratory distress syndrome (ARDS), pneumonia, and multiple organ failure are the severe symptoms in COVID -19 patients. The most common respiratory symptoms were shortness of breath and cough. Most patients have a mild to moderate course of disease and recover without the need for critical treatment. However, in high-risk patients with underlying diseases such as chronic respiratory disease, diabetes, and cardiovascular disease, the infection can lead to a severe syndrome with high mortality.<sup>5</sup> In critically ill patients, hypocalcemia is a common occurrence, with prevalence rates ranging from 15%- 80% in adults. Hypocalcemia has also been associated to the progression of the disease and an increased chance of mortality. In prior studies, hypocalcemia was discovered to be a laboratory abnormality in a number of viral infections.<sup>5</sup>

Due to the high mortality and lack of effective treatments in critical patients, it is critical to identify potential risk factors that can predict clinical development early to stratify the care needed to for patients.<sup>6</sup> The recent literature showed the significant impact of biochemical parameters on COVID-19 severity. The patients admitted in intensive care unit have more imbalanced electrolyte especially hypocalcemia.<sup>5,7,8</sup> Calcium is an important ion in cellular processes, metabolic pathways, and signalling pathways, all of which play a role in virus survival and disease severity.<sup>9</sup>

The hypocalcaemia may be a unique biochemical feature of COVID -19 that has the potential to influence disease severity and represents a new potential therapeutic target worth testing in this clinical setting. Because COVID -19 testing has primarily focused on individuals with respiratory symptoms rather than calcium levels, Therefore the objective of current study was to evaluate the effect of COVID-19 severity on Serum calcium levels.

### METHODOLOGY

After the ethical approval, all the RT-PCR positive patients from the record of corona isolation wards of Ganga Ram hospital Lahore. Demographic details including name, age, gender, complete history & examination serum Calcium level was noted recorded al from hospital files on a predesigned proforma. To assess clinical severity of coronavirus disease, all the enrolled patients' disease category as mild and moderate was note. SPSS-26 was used for data analysis. Association between age and gender between disease severity was determined by using Chi-square test. Binary logistic regression was applied on Disease severity (Mild and Moderate) and other covariates (age and gender) to find out the effect of disease severity on Hypocalcaemia. P-value <0.05 was considered as significant.

### RESULTS

Table 1: Base line history and outcome of patients

Variables	Minimum =11	Maximum =70	38.34+14.86
Age in years			
Age Groups	10-30 Years	31-50 Years	51-70 Years
	185(33.6)	250(45.4)	120(21.8)
Gender	Male	Female	
	300(54.1)	255(45.9)	
Disease severity	Mild	Moderate	
	490(88.3)	65(11.7)	
Outcome	Recovered	Recovered with Ventilator support	
	525(94.6)	30(5.4)	
Serum Calcium mg/dL	Minimum =8	Maximum =10	8.7+0.34

Table 1 shows the Base line history and patient outcome. A total of 555 patients were enrolled in the current study. The age of the patients ranges from 11 and 70 years, respectively. The mean age was 38.34+14.86 Most COVID -19 patients were between 31-50 years 250(45.4). There were 300(54.1) male and 255(45.9) female. The severity of the disease shows that the majority 490(88.3%) of the patients had mild disease and 65(11.7%) had moderate disease. All patients recovered from COVID -19, including 30(5.4) with ventilator support. The mean serum calcium level was 8.7+0.34. The results show that the patients were between 30 and 50 years old and had mild disease severity. All patients recovered and no mortality was reported. Serum calcium was normal in all subjects studied.

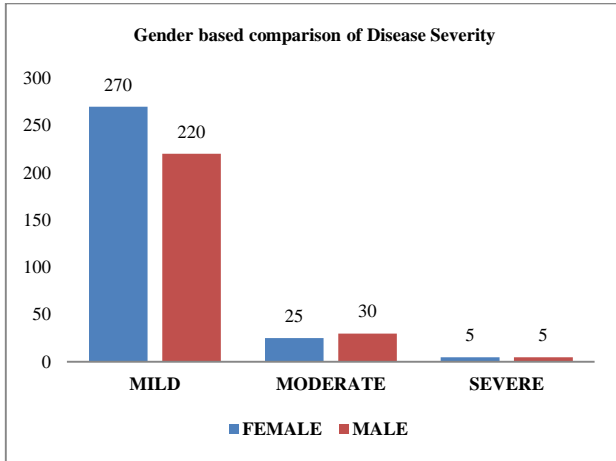


Figure 1: Gender based comparison of Disease Severity

Comparison of disease severity by gender showed that the majority of patients had mild disease, of which 270 were female and 220 male. 25 females and 30 males had moderate disease and severe cases were equally distributed in males and females. (Figure 2)

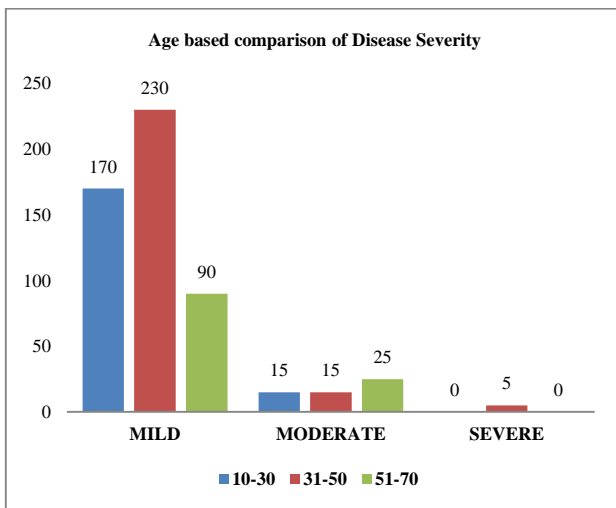


Figure 2: Age based comparison of Disease Severity (P-value<0.05\*\*)

The age-based comparison of disease severity shows that the majority of patients have mild disease, including 170 aged 10-30 years, 230 aged 31-50 years, and 90 aged 51-70 years; in the middle group, 25 patients were 51-70 years old. To some extent, the results suggest that elderly patients have high disease severity. (Figure 3)

Table 2:

Variables in the Equation						
Step 1 <sup>a</sup>	B	S.E.	Wald	df	Sig.	Exp(B)
Calcium	-2.276	.495	21.117	1	.000	.103
Gender(1)	-.701	.309	5.155	1	.023	.496
Age categories			9.180	2	.010	
Age categories(1)	-.700	.377	3.445	1	.063	.496
Age categories(2)	-.987	.333	8.794	1	.003	.373
Constant	18.573	4.280	18.829	1	.000	116456530.081

a. Variable(s) entered on step 1: Calcium, Gender, age categories.

It was reported that the male gender have 0.103 times more chances to have moderate disease as compared to females. As well as the increasing age that is 30-50 years have 0.373 times more chances to have moderate disease. According to disease severity the patients with moderate disease have 0.103 times more chance of having low calcium levels. Calcium level, male and 30-50 years old patients were significant predictors of disease severity. (p-value<0.05)

## DISCUSSION

In 2020 the first case of severe hypocalcaemia in thyroidectomies woman with Covid-19 infection was presented in an 72 years old Italian women. The female was presented with fever, headache, paresthesia and dysarthria. This is the first report of covid-19 infection as a potential risk factor for asymptomatic postoperative hyperparathyroidism with severe hypocalcaemia. The incidence of Hypocalcaemia on hospital admission has been observed in patients with SARS was 60%, usually in mild cases <sup>7</sup> and 62% in patients with Ebola virus disease. <sup>10</sup> For the first time, COVID -19 was suggested as a possible cause of subclinical postoperative hyperparathyroidism. Hypocalcaemia has not yet been identified as one of the major laboratory markers of covid-19 infection. The studies conducted in past epidemic of Ebola and SARS, reported that the most prevalent biochemical abnormality among these patients was hypocalcemia.<sup>7,11</sup>

From August 2014 to December 2015, Uyeki et al documented the clinical characteristics of 27 Ebola virus (EBV) patients treated in the United States and Europe. Total calcium was one of the laboratory indicators measured at the time of admission and during hospitalisation. Hypocalcemia was found in 62% of patients at hospital admission and in 75% of patients during their stay.<sup>11</sup>

The results of current study revealed that total 550 patients were enrolled in the current study. The minimum and maximum ages of the patients were 11 and 70 years, respectively. The mean age of patients was 38.34+14.86. There were 300(54.1) male and 255(45.9) female, majority 490(88.3) of the patients had mild disease and 65(11.7) had moderate disease. The mean serum calcium level was 8.7+0.34. The majority of patients had mild disease, of which 270 were female and 220 male and 230 among 31-50 years. The patients with mild disease have normal serum calcium level.

A case control study was conducted on the patients admitted to emergency department with the possible sign and symptoms of COVID-19 were tested through nasal swab RT-qPCR test. All the biochemistry and hematologic test were performed. The objective of study was to identify the calcium levels among positive and negative patients of COVID-19. It was observed an increased number of patients with low levels of serum total calcium among COVID-Positive patients.<sup>12</sup>

Another retrospective study was conducted in tertiary care hospital of Milan Italy. The objective of the study was to evaluate the ionized calcium levels among COVID positive and negative patients. The results revealed that there was statistical significant difference among both groups. The COVID positive patients have double rate of hypocalcemia.<sup>13</sup>

The results of current study reported that according to disease severity the patients with moderate disease have 0.103 times more chance of having low calcium levels. Calcium level,

male and 30-50 years old patients were significant predictors of disease severity. (p-value <0.05). These findings were supported by various studies that disease severity had significant impact of serum calcium levels.

When patients admitted to the emergency department hypocalcaemia was detected at first evaluation. It was reported that hypocalcaemia is highly associated with the long term hospitalization.<sup>13</sup> In another study it was reported that the low levels of calcium associated with age and Interleukin 6 and C-reactive protein are the risk factors associated with poor outcomes which includes admission at ICUs, ventilator supports and mortality as well.<sup>14</sup>

The comparative study on the calcium levels showed that the hypocalcaemia can lead to septic shock, high oxygen dependency, kidney failure, extensive ventilatory support and kidney failure. These outcomes were more frequent in hypocalcaemia as compared to normocalcemic.<sup>5,9</sup>

COVID -19 patients have severe symptoms such as acute respiratory distress syndrome (ARDS), pneumonia, and multiple organ failure. Shortness of breath and cough were the most common respiratory symptoms. The majority of patients has a mild to moderate course of disease and recover without the need for life-saving therapy. However, the infection can cause a severe course with a high mortality rate in high-risk patients with underlying diseases such as chronic lung disease, diabetes, and cardiovascular disease. Identification of early predictors of clinical severity in COVID -19 patients could lead to better management of disease complications and improve outcomes in high-risk patients.

## CONCLUSION

It was concluded from current study that majority of patients have mild disease severity and patients have normal serum calcium. The disease severity has no significant impact on the calcium levels as the majority of patient has mild disease.

## REFERENCES

- 1 Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. epidemiological, clinical, virological characteristics of 74 cases of coronavirus infection disease 2019(COVID-19) with gastrointestinal symptoms. *GUT*. 2020; 69(6): 1002-1009.

- 2 Gao QY, Chen YX, Fang JY. 2019 novel coronavirus infection and gastrointestinal symptoms. *Journal of digestive diseases*. 2020; 21(3): 125-126.
- 3 Liu J, Han P, Wu J, Gong J, Tian D. Prevalence and predictive value of hypocalcemia in severe COVID-19 patients. *Journal of infection and public health*. 2020. <https://doi.org/10.1016/j.jiph.2020.05.029>.
- 4 Zivin JR, Googley T, Zager RA, Ryan MJ. Hypocalcemia: a pervasive metabolic abnormality in critically ill. *Am J Kidney Dis* 2001;37:689-98.
- 5 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet Infect Dis*. Feb 2020;395(10223):497-506.
- 6 W. Guan, Z. Ni, Hu Yu, W. Liang, C. Ou, J. He, et al. Clinical characteristics of 2019 novel coronavirus infection in China *N Engl J Med*, 2020 (2020).
- 7 Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA*. 2003; 289(21): 2801- 2809.
- 8 Nathan L, Lai AL, Millet JK, et al. Calcium ions directly interact with the Ebola virus fusion peptide to promote structure-function changes that enhance infection. *ACS Infect Dis*. 2019; 6(2): 250- 260.
- 9 Torres B, Alcubilla P, González-Cordón A, Inciarte A, Chumbita M, Cardozo C, Meira F, Giménez M, de Hollanda A, Soriano A, Albiach L. Impact of low serum calcium at hospital admission on SARS-CoV-2 infection outcome. *International Journal of Infectious Diseases*. 2021 Mar 1;104:164-8.
- 10 T.M. Uyeki, A.K. Mehta, R.T. Davey Jr., A.M. Liddell, T. Wolf, P. Vetter, S. Schmiedel, T. Grunewald, M. Jacobs, J.R. Arribas, L. Evans, A.L. Hewlett, A.B. Brantsaeter, G. Ippolito, C. Rapp, A.I. Hoepelman, J. Gutman, Working Group of the U.S.–European Clinical Network on Clinical Management of Ebola Virus Disease Patients in the U.S. and Europe, Clinical management of Ebola virus disease in the United States and Europe. *N. Engl. J. Med.* 374(7), 636–646 (2016)
- 11 Uyeki TM, Mehta AK, Davey RT Jr, et al. Clinical management of Ebola virus disease in the United States and Europe. *N Engl J Med*. 2016;374(7):636–46.
- 12 Cappellini F, Brivio R, Casati M, Cavallero A, Contro E, Brambilla P. Low levels of total and ionized calcium in blood of COVID-19 patients. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2020 Sep 1;58(9):e171-3.
- 13 di Filippo L, Formenti AM, Doga M, Frara S, Rovere-Querini P, Bosi E, Carlucci M, Giustina A. Hypocalcemia is a distinctive biochemical feature of hospitalized COVID-19 patients. *Endocrine*. 2021 Jan;71(1):9-13.
- 14 Sun JK, Zhang WH, Zou L, et al. Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019. *Aging (Albany NY)*. 2020;12(12):11287–95.