Ionic Calcium in Blood as Early Marker of Severity in Patients with COVID-19

Jorge Chung Ching*

Pulmonologist, Arzobispo Loayza Hospital, Respiratory Medicine Service Lima, Perú

Corresponding Author: Jorge Chung Ching, Pulmonologist, Arzobispo Loayza Hospital, Respiratory Medicine Service Lima, Perú.

Abstract

The SARS CoV 2 pandemic has put health systems in serious trouble, especially in Peru, where resources are scarce. The situation is especially difficult for healthcare personnel who have to cope with a disease that is not yet well understood and for which there is no effective treatment. Many of the patients are usually underdiagnosed or misclassified in their state of severity due to the delay in reaching the sum of clinical, analytical and radiological criteria, delaying their treatment and worsening their prognosis. Many authors have reported the finding of low levels of total serum calcium and ionic calcium in severely compromised patients. The determination of ionic calcium has important comparative advantages over serum calcium because the quantification is carried out more quickly and safely, it is not affected by drugs or protein levels and very little by pH, factors that are usually present in COVID-19 patients. The present work ionic calcium in blood as early marker of severity in patients with covid-19 at the arzobispo loayza national hospital of Lima-Perú seeks to contribute to the knowledge showing that ionic calcium can be an early marker of severity in hospital emergency rooms severity, allowing a correct classification of the disease in less time, improving action protocols, saving material and human resources and above all saving valuable lives.

Keywords: *Ionic Calcium; Blood; Patients; COVID-19; C-Reactive Protein*

Abbreviations

SPN: Sociedad Peruana De Neumología Member; ATS: American Thoracic Society Member; ERS: European Respiratory Society Member; ALAT: Asociación Latinoamericana Del Tórax Member

Background

For health personnel COVID-19 has been especially difficult to face a new disease against which there were neither control measures nor effective treatments [1-4]. In this situation, the finding of inflammatory markers that could guide clinicians about the severity of the infectious disease [5-7] and the possibility of predicting mortality in some way would undoubtedly constitute the cornerstones on which the rest of the actions would be based with a view to recovering patients who crowd health services, saving resources and saving human lives [8-10].

This work focuses on the study of Ionic Calcium (Ca^{2+}) as a marker of both disease severity upon admission to the health service, as well as imminent death because it can be measured very quickly and precisely as part of the gas arterial analysis [11,12].

Summary

To determine whether Ionic Calcium (Ca^{2+}) in blood is a good marker of the severity of COVID-19 pictures, as well as an independent predictor of mortality, a study was carried out with patients diagnosed with this disease at the Arzobispo Loayza National Hospital (HNAL) in Lima-Peru admitted to hospitalization.

Materials and Methods

The selected sample consisted of 200 cases of patients diagnosed by molecular tests and who required hospitalization for medical management. Examinations of biochemical and hematological inflammatory markers were collected on admission and the data were analyzed using correlation tests and binomial logistic regression.

Results. In the logistic regression, the level of Ca^{2+} shows a good relationship with the severity of COVID-19 cases, which can be a marker of severity ($p < 0.05$) as well as ferritin, C-reactive protein, D-dimer and the Kirby index. In the same type of statistical test, a non-significant relationship between Ca^{2+} and death was observed ($p > 0.05$). The Kaplan-Meier study also did not show a significant relationship between Ca^{2+} and survival.

Conclusions. The Ca^{2+} level is a good marker to determine the severity of the disease ($p < 0.05$) as well as ferritin, C-reactive protein, D-dimer and the Kirby index; but it is not significantly related to death in this group of patients in the context of the current SARS-CoV2 pandemic.

We included 200 cases of patients diagnosed by molecular tests for COVID19 upon admission to hospital emergency rooms selected in a simple random sampling and classified by state of severity according to current regulations. In each case, samples were taken for tests that included basic blood tests, inflammatory markers, and arterial gases that included ionic calcium. For this study, the determination of COVID-19 and its severity followed the parameters described by WHO and Peruvian Ministry of Health [13,14]. The diagnosis of SARS-CoV-2 was made or endorsed by the national reference laboratory (National Institute of Health of Peru).

As a first step in the analysis, a crossover was made between the variables state of severity and destination. Binomial logistic regression was performed to determine the relationship between ionic calcium level and severity. The same processing was carried out to relate the inflammatory markers with the outcome.

Finally, we performed Kaplan-Meier analysis to observe relationship between Ca^{2+} levels and mortality.

The entire statistical process was performed in SPSS 25.0® (SPSS, Inc., Chicago, Ill., USA). Findings were considered significant if they reached a p value < 0.05.

Ethical aspects

All actions, procedures, and interventions respected the ethical standards approved by the hospital and regulated by the Ethics Committee, following the standards of the Declaration of Helsinki.

Results

200 cases were studied, 74 women among whom 56 were in serious condition and 126 men of which 100 were admitted with the same condition. Under 60 years were 96 patients and women and over 60 years were 104 patients between men and women. During the follow-up time of the cases, 125 patients were discharged and 75 died from causes associated with COVID-19 and its complications (Table 1).

Female		Sex	
		Male	
Age	Under 60 y	28	68
	Above 60 y	46	58
Gravity	Non-Severe	18	26
	Severe	56	100
Outcome	Discharge	47	78
	Death	27	48

Table 1: *Frequency and Distribution Table.*

As a first step in the analysis, a crossover was made between the variables state of severity and destination, finding that 92.8% of deceased patients were considered in serious condition upon admission to the emergency room (Table 2). This is of particular interest because it reinforces the need to establish the status of patients quickly and reliably upon admission to improve the actions of the emergency services.

Discharge			Outcome		Total
Death					
Gravity	Non severe	N	38	6	44
		%	30.4%	7.2%	21.2%
	Severe	N	87	69	156
		%	69.6%	92.8%	78.8%
Total		N	125	83	200
%		100.0%	100.0%	100.0%	

Table 2: Gravity-Destination Correlation.

Binomial logistic regression was performed to determine the relationship between inflammatory markers and severity, observing that the level of ionic calcium is related to the severity of the cases, being statistically significant, as are the values of C-Reactive Protein, D-Dimer, Ferritin and the Kirby index (PaO_2/FIO_2).

		Punctuation	gl	P
Variables	C-reactive protein	26.631	1	0.000
	D-dimer	56.909	1	0.000
	Ferritin	6.253	1	0.012
	Ca^{2+}	36.278	1	0.000
	Pa/fio_2 (kirby index)	35.652	1	0.000

Table 3: Binomial Logistic Regression between inflammatory markers and severity.

Likewise, the same processing was carried out to relate the inflammatory markers with the outcome, observing that there is no relationship between the levels of ionic calcium with the destination (discharge or death). In this analysis there were no significant differences ($p > .05$) for Ca^{2+} but there were strong relationships between death and the levels of Ferritin, C-Reactive Protein, D-Dimer and the Kirby Index ($PaFIO_2$).

		Punctuation	gl	P
Variables	C-reactive protein	19.544	1	0.000
	D-dimer	25.312	1	0.000
	Ferritin	18.831	1	0.000
	Ca^{2+}	2.339	1	0.126
	Pa/fio_2 (kirby index)	27.149	1	0.000

Table 4: Binomial Logistic Regression between inflammatory markers and Outcomes.

In addition, the Kaplan-Meier survival analysis was performed with discrimination using the Log-Rank test to determine whether calcium levels are related to mortality.
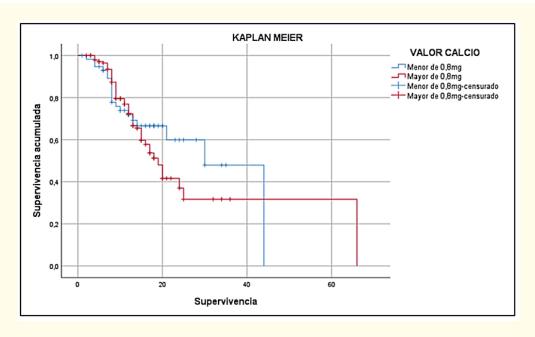
Ca2+ level	Mean				Median			
	Estimation	Desv. Error	Ci 95%		Estimation	Desv. Error	Ci 95%	
			Lower límit	Upper límit			Lower límit	Upper límit
Under 0,8mg%	28.861	2.931	23.116	34.607	30.000	4.918	20.360	39.640
Above 0,8 mg%	30.865	3.807	23.404	38.326	19.000	1.551	15.960	22.040
Global	31.420	3.503	24.555	38.285	21.000	2.622	15.862	26.138

Table 5: Survival Analysis.

The statistical analysis shows that there are no significant differences between patients with low or normal ionic calcium values and death. Nor are there significant differences in the plot of the Kaplan-Meier curve (Graph 1).

	Chi-Square	gl	P
Log Rank (Mantel-Cox)	0.614	1	0.433

Table 6: Global Comparisons.

Graph 1: Kaplan-Meier Survival Curve.

Discussion

In several studies, the relationship between hypocalcemia and higher mortality was found, as well as worse clinical outcome in hospitalized and critically ill patients [15-19]. Despite the abundant literature available, there are still no conclusive data on calcium levels in this infectious disease [6,7,11,12,14-19,21].

In the present study, patients with an admission diagnosis of SARS-CoV-2 were selected, who were classified as Serious and Non-Serious [13], and were followed up until their final outcome, both at discharge and at death. The observed Ca^{2+} levels were more reliable than total serum calcium in part because we used serum ionized calcium levels, a better measure than albumin-corrected total calcium levels [15-18].

It was established that there is a true correlation between the state and the outcome with a percentage. This finding, on the one hand, confirms the premise that severe cases lead to inexorable death if not treated in time [22-24] and, on the other hand, makes efforts to identify an early and easy-to-measure marker of severity more urgent and important. In the middle of such a scenario is the determination of Ca^{2+}, which is reported within the arterial gas analysis upon admission to the emergency room to determine the need for oxygen therapy. This data goes unnoticed and is not considered, despite being available and easily accessible [11,12].

The statistical analysis showed that Ca^{2+} turns out to be a good marker of severity at admission, as well as C-Reactive Protein, D-Dimer, Ferritin and Kirby's Index (PaO_2/FiO_2) [6,7,10], so it can be used when the other parameters and studies requested are not available, which can take hours or days in the reality of this hospital, saving time and important resources.

However, when doing the same processing to relate Ca^{2+} with the death of the patients, we found that there was no significant difference between the measured Ca^{2+} values and the destination, both at discharge and at death.

The Kaplan Meier analysis with Mantel Cox discrimination comparing 2 groups of patients by Ca^{2+} levels (low and normal) did not show significant differences.

This bad relationship can be due to multiple factors such as the treatment received and the delay time in the intervention [19,25-28].

Conclusions

Ca^{2+} is an easily measurable ion that is usually included in the blood gas analysis performed in the hospital emergency department at the time of admission of patients with SARS-CoV-2. This data often goes unnoticed compared to the importance given to pH and the concentration of oxygen and carbon dioxide in arterial blood (PO_2 and PCO_2), but it has great relevance in the evaluation in many pathological states. Observations from different studies have focused on total calcium, but this is more difficult to determine and usually requires a special order from the medical team at the Arzobispo Loayza hospital and therefore takes too long. For these reasons the determination of Ca^{2+} offers enormous advantages [11,12,15-18].

In light of the findings of the present study, it is observed that the determination of ionic calcium is useful to identify severe SARSCoV2 cases and with imminent complications upon admission to hospitalization at Loayza hospital. This could improve care protocols by providing specialized support in less time and with significant savings in financial and human resources. However, it is not useful as a predictive marker of death in the same group of patients, therefore it should not be taken into account independently or in isolation from other markers to assess the prognosis of death [8,9,20,29-32].

Despite the fact that the Archbishop Loayza Hospital is one of the largest and most representative in Peru, the population studied is relatively small compared to the total number of admitted to the different hospitals in the country, so studies with a larger population and preferably multicenter are needed for a better definition of the utility of Ca^{2+} in SARSCoV2.

Conflict of Interest

The authors have no conflicts of interest.

Bibliography

1. OMS. "Coronavirus disease (COVID-19) Situation Report-113" (2020).

2. Chen B., *et al.* "Overview of lethal human coronaviruses". *Springer Nature* (2020): 5.

3. Little P. "Non-steroidal anti-inflammatory drugs and covid-19". *BMJ* 368 (2020).

4. "COVID-19 Latin America and the Caribbean" (2020).

5. Douedi S and Miskoff J. "Novel coronavirus 2019 (COVID-19)". *Medicine Baltimore* 99.19 (2020): e20207.

6. Chen N., *et al.* "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". *Lancet* 395 (2020): 507-513.

7. Huang C., *et al.* "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 395.10223 (2020): 497-506.

8. Wang D., *et al.* "Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China". *The Journal of the American Medical Association* 323.11 (2020): 1061-1069.

9. Arentz M., *et al.* "Characteristics and Outcomes of 21 Critically Ill Patients with COVID-19 in Washington State". *American Medical Association* 323 (2020): 612-614.

10. Leisman DE., *et al.* "Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes". *Lancet Respiratory Medicine* (2020): 11

11. Lippi G and Plebani M. "Laboratory abnormalities in patients with COVID-2019 infection". *Clinical Chemistry and Laboratory Medicine* 58 (2020): 1131-1134.

12. Lippi G and Plebani M. "Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis". *Clinica Chimica Acta* 55 (2020): 190-191.

13. Ministerio de Salud del Perú. RM 972-2020-MINSA. Manejo de personas afectadas COVID-19 en servicios de hospitalización (2020).

14. Tenforde MW., *et al.* "Characteristics of Adult Outpatients and Inpatients with COVID-19 - 11 Academic Medical Centers, United States" 69.26 (2020): 841-846.

15. Filippo L Di., *et al.* "Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19". *Endocrine* 68 (2020): 475-478.

16. Sun J-K., *et al.* "Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019: a retrospective cross-sectional study". *Aging* 12.12 (2020): 11287-11295.

17. Liu J., *et al.* "Prevalence and predictive value of hypocalcemia in severe COVID-19 patients". *Journal of Infection Public Health* 13 (2020): 1224-1228.

18. Cappellini F., *et al.* "Low levels of total and ionized calcium in blood of COVID-19 patients". *Clinical Chemistry and Laboratory Medicine* 58.9 (2020): 171-173.

19. Tenforde MW., *et al.* "Characteristics of Adult Outpatients and Inpatients with COVID-19 -11 Academic Medical Centers, United States" 69.26 (2020): 841-846.

20. Myers LC., *et al.* "Characteristics of Hospitalized Adults with COVID-19 in an Integrated Health Care System in California". *Journal of the American Medical Association* 323 (2020): 2195-2198.

21. Cummings MJ., *et al.* "Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study". *Lancet* 395.10239 (2020): 1763-1770.

22. Dillinger JG., *et al.* "Coronary Artery Calcification and Complications in Patients with COVID19". *Journal of the American College of Cardiology Imagining* 11 (2020): 2468-2470.

23. Stokes EK., *et al.* "Coronavirus Disease 2019 Case Surveillance -United States" 69.24 (2020): 759-765.

24. Morris SB., *et al.* "Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection -United Kingdom and United States, March-August 2020". *Morbidity and Mortality Weekly Report* 69.40 (2020): 1450-1456.

25. Zhou F., *et al.* "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study". *Lancet* 395.10229 (2020): 1054-1062.

26. Wu C., *et al.* "Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China". *JAMA Internal Medicine* 180.7 (2020): 934-943.

27. Shi S., *et al.* "Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China". *JAMA Cardiology* 5.7 (2020): 802-810.

28. Richardson S., *et al.* "Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area". *JAMA - The Journal of the American Medical Association* 323.20 (2020): 2052-2059.

29. Meyerowitz-Katz G and Merone L. "A systematic review and meta-analysis of published research data on COVID-19 infection-fatality rates". *International Journal of Infectious Diseases* (2020): 101.

30. Kurdi B., *et al.* "Mortality from Coronavirus Disease 2019 Increases with Unsaturated Fat and May Be Reduced by Early Calcium and Albumin Supplementation". *Gastroenterology* 159.3 (2020): 1015-1018.

31. Rodriguez-Morales AJ., *et al.* "COVID-19 in Latin America: The implications of the first confirmed case in Brazil". *Travel Medicine and Infectious Disease* 35 (2020): 101613.

32. Weiss P and Murdoch DR. "Clinical course and mortality risk of severe COVID-19". *Lancet* 395 (2020): 1014-1045.