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pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en D.E.S de gériatrie

Association between ionized calcium and two-year mortality in geriatric patients hospitalized for COVID-19

Etude de l'association entre la calcémie ionisée et la mortalité a deux ans chez les personnes âgées atteintes de la COVID-19

BOUDAILLE Audrey

Née le 05 juin 1996 à Metz (57)

Sous la direction du Dr BOURGEAIS Alexis

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« Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité. Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité. J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences. Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

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Liste des abréviations

[illegible]

Plan

LISTE DES ABREVIATIONS

ABSTRACT

INTRODUCTION

MATERIAL AND METHODS

1. Study population

2. Biological data and COVID-19 diagnostic

3. Covariates

4. Overall mortality

5. Statistical analysis

6. Ethics

RESULTS

1. Clinical characteristics of the population

2. Association between CaI and two-year mortality

DISCUSSION

CONCLUSION

BIBLIOGRAPHY

LISTE DES FIGURES

LISTE DES TABLEAUX

TABLE DES MATIERES

ABSTRACT

Introduction. Coronavirus disease 2019 (COVID-19) has caused hundreds of thousands of deaths since it was first identified in 2019. Measure of ionized calcium (CaI) are the gold standard, is not routinely measured, as it is a complex process. Hypercalcemia is known to cause diffuse symptoms that can lead to death. The aim of this quantitative, descriptive study is to determine an association between ionized calcium and death two years after Covid-19 infection in geriatric population.

Methods. One hundred and seventy-nine patients hospitalized in the geriatric acute care unit of Angers University Hospital were included in the study. Their data were analyzed between the 1st March 2020 and 29 March 2021. Covid-19 infection was diagnosed by viral PCR or chest CT scan. Ionized calcium levels were determined by potentiometry. Covariates considered were: age, sexe, GIR score ≤ 3 , PTH, CRP, severe undernutrition, history of cancer, history of cardiomyopathy, severe chronic renal failure (defined as clearance < 30 ml/min) and OCSI score. The time elapsed between the diagnosis of COVID-19 and death was studied by survival curves calculated using the Kaplan-Meier method in each group defined by serum CaI concentration (> 1.19 and ≤ 1.19 mmol/L) and compared by log-rank.

Results. In the Cox model, a significant association was found between ionized calcium over 1.19 mmol/l and 2-year mortality, whether analyzed in an unadjusted model (HR 1.54 [1.04-2.29], $p = 0.032$) or adjusted model (HR = 1.71 [1.12-2.61], $p = 0.014$). A GIR score ≤ 3 , severe undernutrition and an OSCI score ≥ 6 were associated with 2-year mortality in both models.

Conclusions. There is an association between ionized calcium over 1.19 mmol/l and two-year mortality in geriatric patients hospitalized for COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has caused hundreds of thousands of deaths since it was first identified in Wuhan, China, in December 2019 (1). This viral infection mainly affects the respiratory system. According to various studies, older age and common comorbidities worsen the prognosis of COVID-19 patients (2,3). Since 2019, dyscalcemia has been established as a potential prognosis factor (4).

Circulating calcium accounts for 0.07% of total calcium. There are two measurable forms: ionized calcium (40-50%) and calcium bound to proteins (50-60%), especially to albumin (5). However, it remains the gold standard, ionized calcium (CaI) is not routinely measured, as it is a complex and costly process (6). Calcium ion acts as a second messenger within cells, notably for the cell and apoptosis. Abnormalities in calcium signaling could be involved in the development of chronic diseases, in particular cardiovascular disease (7).

Ionic disorders such as dyscalcemia have been observed in bacterial, viral pneumonia, particularly in cases of SARS-CoV virus and Ebola (8–10). The virus uses calcium for many aspects of the replication cycle. Active uptake of calcium ions by mitochondria increase ATP production to meet the increased energy demands of continuous viral replication (11). SARS-CoV is composed of an E protein which stimulate the NF- κ B inflammatory pathway (12). The SARS-CoV E protein uses calcium ions to activate the NLRP3 inflammasome, leading to IL-1 β overproduction. This leads to a large inflammatory response, which could explains the lung damage (13). *Xu Qi et al.* (2021) demonstrated that the serum Ca²⁺ levels of COVID-19 patients were significantly correlated with coagulation dysfunction (14). Hypocalcemia was also found to be negatively correlated with inflammatory factors, and associated with increased in-hospital mortality (15,16).

Only few studies have questioned the role of normal-to-high calcium concentration in context of COVID-19. In 2021, an Angers University Hospital study found that a normal-to-high calcium

concentration, estimated early in COVID-19 from corrected calcium levels, was associated with higher 3-month mortality in frail older patients (17). In this context, we aimed to investigate the association between normal-to-high ionized calcium levels and 2-year mortality in frail older patients with COVID-19.

MATERIAL AND METHODS

A quantitative, descriptive, retrospective study based on the GERIA-COVID database was performed. GERIA-COVID database was carried out in the geriatric acute care unit dedicated to COVID-19 patients in the University Hospital of Angers, France (ClinicalTrials.gov NCT04560608).

1. Study population

The inclusion criteria in the GERIA-COVID study were as follows (figure 1):

- 1) Patients aged 75 years and over hospitalized in the geriatric acute care unit of Angers University Hospital, France, between 1st March 2020 - 30 June 2020 and 1st October 2020 – 29 march 2021;
- 2) No objection from the patient and/or relatives to the use of anonymized clinical and biological data for research purposes

The inclusion criteria for the present analysis were as follows:

- 1) COVID-19 diagnosed with RT-PCR and/or chest CT-scan;
- 2) Data available on ionized calcium, albumin and Parathyroid hormone (PTH) at hospital admission;
- 3) Data available on the vital status 2 years after COVID-19 diagnosis.

Patients with missing data were excluded.

2. Biological data and COVID-19 diagnostic

Blood samples were collected on admission to the geriatric acute care unit. All biological samples were analyzed at the biology department of the University Hospital Angers. COVID-19 was diagnosed with RT-PCR and/or chest CT-scan. CaI was collected with a blood gas syringe and analyzed using blood gas machine from the first of March 2020 to the 29th of November then by direct potentiometry (ABL 90 Flex plus or ABL 800) from the 30th of

November 2020 to the 29th of March 2021. This measurement was systematically adjusted to pH. PTH and 25(OH)D were measured with an immunoassay method (Automate LiaisonXL, DiaSorin). C-Reactive Protein (CRP) and albumin were measured with immunoturbidimetric method (Advia Chemistry XPT, Siemens). Calcemia were measured with colorimetric method. Glomerular filtration rate has been estimated with Modification of Diet in Renal Disease.

3. Covariates

Age, sexe, Iso-Resources Groups (GIR) score ≤ 3 (measured from 1 to 6 (best)), PTH, CRP, severe undernutrition (defined as an albuminemia inferior to 30 g/L), history of cancer, history of cardiomyopathy, severe chronic renal failure (defined as clearance < 30 mL/min), COVID severity (defined as an Ordinal Scale for Clinical Improvement (OSCI) score $\geq 6/8$). An OSCI score of 6 corresponds to an intubated patient.

4. Overall mortality

Main outcome was 2-year all-cause mortality. Follow-up began on the date of COVID-19 diagnosis for each patient. Vital status after 2 years was recovered by monitoring the National Institute of Statistics and Economic Studies (INSEE) register (<https://www.insee.fr/fr/information/4190491>).

5. Statistical analysis

A descriptive analysis of the participant's characteristics was firstly performed using numbers (percentages) for qualitative variables and means $\pm$ standard deviations or medians [inter-quartile range (IQR)] for quantitative variables, as appropriate. Firstly, comparisons between participants separated according to the vital status at the end of years 2 of the diagnosis of COVID-19 were performed using Chi-square test (or Fisher exact test) or Student t test (or Mann-Whitney Wilcoxon test according to the normality assessment), as appropriate.

Secondly, univariate Cox regression models were used to examine the associations of 2-year mortality (dependent variable) with baseline clinical and biological characteristics (independent variables), including CaI. All of these variables of interest were then included in a multivariate Cox regression model. Finally, the elapsed time from COVID-19 diagnosis to death were studied by survival curves computed according to Kaplan-Meier method in each group defined by the serum concentration of CaI (> 1.19 and ≤ 1.19 mmol/L) and compared by log-rank test. P-values <0.05 were considered significant. All statistics were performed using SAS® version 9.4 (SAS Institute Inc.) and R (R Core Team, V 4.3.1, 2023).

6. Ethics

The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). No participant or relatives objected to the use of anonymized clinical and biological data for research purposes. Ethics approval was obtained from the Ethics Board of the University Hospital of Angers, France (2020/100). The study protocol was also declared to the National Commission for Information Technology and civil Liberties (CNIL; ar20-0087v0).

RESULTS

1. Clinical characteristics of the population

Of the 179 participants, 90 have an CaI ≤ 1.19 mmol/l and 89 have an CaI > 1.19 mmol/l.

Table 1 shows the characteristics of the participants according to the study group.

A total of 179 patients were included in this study, including 90 women (50.3%), mean age was 86.4 ± 5.7 years. Sixty-two patients suffered from severe denutrition among the participants (34.6%), 34 (19%) have history of cancer, 56 (31.3%) history of cardiomyopathy and 29 (16.2%) suffered from severe chronic renal failure. The median of PTH were 29.7 [18.7-43.6] pg/ml, the median of CRP was 63.0 [29.0-119.0] mg/l. Fifty-three participants (29.6%) have OSCI score ≥ 6 (**Table I**).

2. Association between CaI and two-year mortality

In Cox proportional-hazards models, a significant association was found between serum ionized calcium concentration > 1.19 mmol/l and 2-year mortality whether analyzed in unadjusted model (HR 1.54 [1.04-2.29], $p = 0.032$) or fully-adjusted model (HR = 1.71 [1.12-2.61], $p = 0.014$) (**Table II**). GIR score ≤ 3 , severe denutrition, and OSCI ≥ 6 were also associated with 2-year mortality in unadjusted model (respectively, $p < 0.001$, $p = 0.044$ and $p < 0.001$) and remained significant in the fully-adjusted model (respectively, $p = 0.02$, $p = 0.027$ and $p < 0.001$). Age, history of cardiomyopathy, severe chronic renal failure, serum PTH concentration and serum CRP concentration was associated with 2-year mortality in unadjusted model but not in the fully-adjusted model.

Serum ionized calcium concentration > 1.19 mmol/l, GIR score ≤ 3 , history of cardiomyopathy, history of cancer and OSCI ≥ 6 were associated with 2-year mortality in model with backward selection (respectively, $p = 0.028$, $p < 0.001$, $p = 0.012$, $p < 0.001$ and $p < 0.001$).

Kaplan-Meier distributions showed in **Figure 2** that COVID-19 patients with serum ionized calcium concentration > 1.19 mmol/l had shorter survival time than those with normocalcemia (log-rank $P=0.0302$).

DISCUSSION

Two-year mortality was significantly more frequent in the group with CaI over 1.19 mmol/l, in geriatric population with COVID-19, regardless of frailty, severe denutrition, initial severity and comorbidities.

Mitochondria and calcemia have a strong interaction. Entry of calcium into mitochondria is involved in the production of ATP (11). Many receptors were known to be involved in the entry and exit of calcemia from the cell, including mitochondrial K^+/H^+ exchanger and Na^+/Ca^{2+} exchanger. However, a massive influx of calcium into the cell causes cell necrosis (18). Mitochondrial dysfunction resulting from modification in the intestinal microbiota could be partly responsible for long COVID (19). We could hypothesize that a mitochondrial dysfunction could result from the normal to high calcemia inducing this poor prognosis in this patient.

Another hypothesis to explain this result could be the impact of cardiovascular risk after COVID-19. Elastin is a protein responsible for the elasticity of many human organs. *Yang* and al found that calcium ions and glucose can interact with tropoelastin and stiffen the artery. As a result, soft tissues such as cardiovascular and lung tissue become stiffer in hypercalcemia. This tends to accelerate the onset or aggravate frailty, particularly in the older patients whose elastin is already impaired by physiological aging (20). In the elderly patients, we can assume that the increased cardiovascular risk partly explains the higher 2-year mortality rate in COVID-19. The mechanism depends on the function of a sodium cotransporter, but this remains poorly defined (21,22).

Calcemia can be exacerbated by immobilization, particularly in the older patients, and by isolation in a room for several days (23). This was particularly the case in the first wave in France, as room visits, including physiotherapy, were limited. Immobilization could increase the frailty of older patients (24). This may partly explain the high trend in calcemia in the cohort patients.

SARS-CoV-2 infection also increased frailty and cardiovascular risk in older patients, notably by reducing physical activity and increasing sedentary time (25). Various factors can also influence the frailty of older patients affected by COVID-19, such as lockdown or direct and long term (26).

Independent association between CaI and mortality have been studied in hospitalized patients regardless of diagnosis. A U-shaped relationship is observed, indicating the importance of high and low trends in calcemia (15,27). *Thongprayoon et al.* assessed that CaI levels were correlated with hospital mortality and 1 year mortality. The upper limit of CaI for increased in-hospital and 1-year mortality was ≥ 5.20 mg/dl (1.297 mmol/l). Hypercalcemia seems to be less lethal than hypocalcemia (15). *Cheungpasitporn et al.*, found that an association between admission hypocalcemia or hypercalcemia serum (≥ 2.52 mmol/l) with an increased risk of in-hospital mortality. A third of patients of this patients were taking calcium supplements on admission (27).

In the population with stable coronary artery disease, all-cause mortality and cardiovascular mortality are significantly higher in the high calcemia group ($\text{Ca} \geq 2.72$ mmol/l) (28). Calcemia was measured in 1017 patients. The patients were between 30 and 70 years old. Hypercalcemia increases the risk of cardiovascular disease, in particular with a positive association in blood pressure and blood cholesterol levels (29).

Corrected calcium report increased mortality at three months in COVID patients with calcium over 2.5 mmol/L (17). Conversely, *Yang et al.* found no association between normal to high blood calcium levels and severe to critical forms of COVID-19, but the association is present with a calcium concentration below than 2.11 mmol/l (30).

Certain limitations need to be emphasized. First, a majority of hospital admissions took place in winter. In this period, co-infection is possible and has not been considered in our study. Secondly, vaccination is not taken into account, which could influence initial and long-term

consequences. Thirdly, the study focuses on the first wave of patients. COVID-19 was poorly understood at that time and the variants were different from today. Since then, the therapeutic strategy has evolved, thanks to the use of antivirals. Fourth, different analyzers were used during the studies. However, direct potentiometry was used in both cases. In addition, the CaI of the majority of patients was analyzed by the second analyzer (31). Fifth, we did not take into account vitamin D supplementation, calcium supplementation, or the influence of different treatments. Calcium supplementation could have an effect on long-term mortality due to the possible effect on cardiovascular risk and the development of neurocognitive disorders (32,33). The strengths of our study are a robust primary endpoint, which is death. We used ionized calcium measurement, which remains the gold standard, and few studies have focused on this measurement of blood levels in COVID-19. Moreover, using CaI in older patients is an original prognostic factor. Few studies have taken normal-to-high values into account, and not just strict hypercalcemia, which challenge the interpretation of normal calcemia in the context of COVID-19. More studies on new form of SARS-CoV-2 is necessary to draw definitive conclusions on the results of this study.

CONCLUSION

In conclusion, there is an association between CaI and two-year mortality in geriatric patients hospitalized for COVID-19. Mortality was significantly higher in the group with CaI over 1.19 mmol/l. Few studies have taken normal-to-high values into account, and not just strict hypercalcemia, which challenge the interpretation of normal calcemia in the context of COVID-19.

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LISTE DES FIGURES

Figure 1	17
Figure 2	18

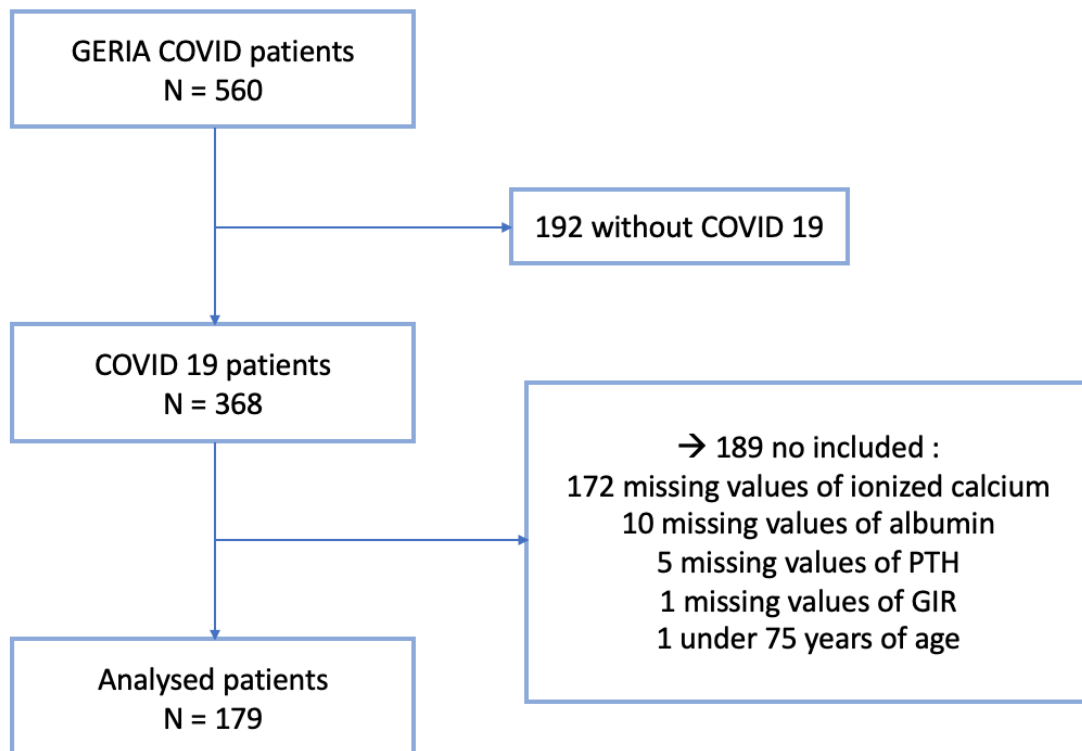


Figure 1. Flow Chart

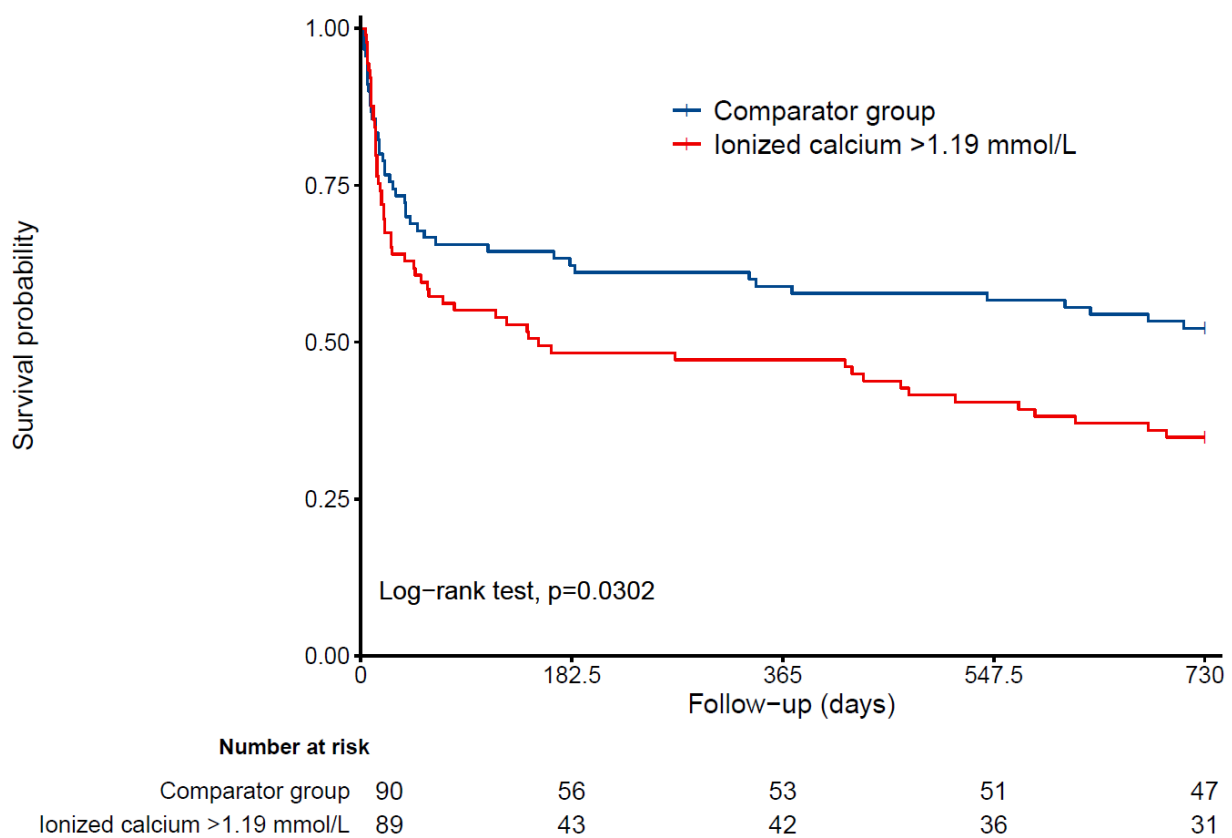


Figure 2. Kaplan-Meier estimates of the cumulative probability of COVID-19 participants' survival according to Serum ionized calcium concentration (n=179).

LISTE DES TABLEAUX

Table I.....	20
Table II.....	21

Table I. Characteristics and comparisons of COVID-19 patients separated into two groups according to the study group (n=179).

	Total cohort (n=179)	Study group		P-value*
		Ionized calcium	Ionized calcium	
		≤ 1.19 mmol/L (n=90)	> 1.19 mmol/L (n=89)	
Demographical data				
Age (years), mean±E.T	86.4±5.7	85.8±5.2	87.0±6.2	0.173
Female sex	90(50.3)	42(46.7)	48(53.9)	0.331
GIR score ≤ 3	105(58.7)	57(63.3)	48(53.9)	0.202
Comorbidities				
Severe undernutrition	62(34.6)	34(37.8)	28(31.5)	0.375
History of cancer	34(19.0)	21(23.3)	13(14.6)	0.137
History of cardiomyopathy	56(31.3)	24(26.7)	32(36.0)	0.180
Severe chronic renal failure	29(16.2)	18(20.0)	11(12.4)	0.165
Hospitalization				
OSCI ≥ 6	53(29.6)	25(27.8)	28(31.5)	0.589
Serum PTH concentration (pg/ml), med[IQ]	29.7[18.7-43.6]	31.3 [18.6-45.4]	26.8 [19.1-37.2]	0.377
Serum CRP concentration (mg/L), med[IQ]	63.0 [29.0-119.0]	68.0 [34.0-156.0]	58.0 [22.0-94.0]	0.087
Follow-up				
2-year mortality	101(56.4)	43(47.8)	58(65.2)	0.019

Data presented as n (%) where applicable; COVID-19: Coronavirus Disease 2019; CRP: C-Reactive Protein; GIR: Iso Resource Groups; OSCI: Ordinal Scale for Clinical Improvement; PTH: Parathyroid hormone *: between-group comparisons based on Chi-square test (or Fisher exact test) or Student t test (or Mann-Whitney Wilcoxon test), as appropriate;

Table II. Multiple Cox proportional-hazards model showing the hazard ratio for 2-year mortality (dependent variable) among COVID-19 patients according to Serum ionized calcium concentration (independent variable), adjusted for potential confounders (n=179).

	2-year mortality					
	Unadjusted model		Fully-adjusted model		Model with backward selection method	
	HR [95% CI]	P-value	HR [95% CI]	P-value	HR [95% CI]	P-value
Serum ionized calcium concentration > 1.19 mmol/L	1.54[1.04-2.29]	0.032	1.71[1.12-2.61]	0.014	1.58[1.05-2.38]	0.028
Age	1.07[1.04-1.11]	<0.001	1.04[0.99-1.09]	0.054		
Female sex	0.72[0.49-1.07]	0.103	0.74[0.48-1.13]	0.159		
GIR score ≤ 3	2.82[1.82-4.40]	<0.001	2.17[1.33-3.55]	0.002	2.52[1.59-3.98]	<0.001
Severe undernutrition	1.05[0.69-1.58]	0.044	0.60[0.38-0.94]	0.027		
History of cancer	1.18[0.73-1.91]	0.505	1.84[1.10-3.10]	0.021	1.89[1.15-3.10]	0.012
History of cardiomyopathy	2.09[1.41-3.11]	<0.001	1.46[0.90-2.38]	0.125	2.19[1.46-3.28]	<0.001
Severe chronic renal failure	2.86[1.81-4.52]	<0.001	1.22[0.67-2.20]	0.511		
OSCI ≥ 6	10.42[6.72-16.16]	<0.001	12.86[7.50-22.08]	<0.001	11.42[7.03-18.54]	<0.001
Serum PTH concentration (pg/ml)	1.008[1.003-1.012]	0.002	1.004[0.998-1.009]	0.240		
Serum CRP concentration (mg/L)	1.003[1.001-1.006]	0.025	1.002[0.999-1.006]	0.192		

CI: confidence interval; CRP: C-Reactive Protein; GIR: Iso Resource Groups; OSCI: Ordinal Scale for Clinical Improvement; PTH: Parathyroid hormone; HR: hazard ratio;

TABLE DES MATIERES

ABSTRACT	1
INTRODUCTION.....	2
MATERIAL AND METHODS	4
RÉSULTS.....	7
DISCUSSION	9
CONCLUSION.....	12
BIBLIOGRAPHY	13
LISTE DES FIGURES.....	16
LISTE DES TABLEAUX	19
TABLE DES MATIERES.....	22

BOUDAILLE Audrey

Etude de l'association entre la calcémie ionisée et la mortalité à deux ans chez les personnes âgées atteintes de la COVID-19

RÉSUMÉ

Introduction. L'infection à COVID-19 a causé des centaines de milliers de décès depuis sa mise en évidence en 2019. La mesure de la calcémie ionisée reste le gold standard, même si celle-ci est couteuse et difficile à réaliser. L'hypercalcémie est connue pour donner des atteintes diffuses et de multiples symptômes pouvant aller jusqu'au décès. L'objectif de cette étude quantitative, descriptive, est de déterminer une association entre calcémie ionisée et décès à deux ans d'une infection à Covid-19, dans notre population gériatrique.

Matériel et méthodes. Cent soixante-dix-neuf patients hospitalisés dans le service de gériatrie aiguë au CHU d'Angers, ont été inclus dans l'étude. Leurs données ont été analysées entre le 1^{er} mars 2020 et le 29 mars 2021. L'infection à Covid-19 a été diagnostiquée par PCR virale ou scanner thoracique. Le dosage de la calcémie ionisée a été effectué par potentiométrie. Les covariables prises en compte sont : l'âge, le sexe, le score GIR ≤ 3 , la PTH, la CRP, la dénutrition sévère, les antécédents de cancer, les antécédents de cardiomyopathie, l'insuffisance rénale chronique (définie par une clairance < 30 ml/min) et le score OSCI. Le temps écoulé entre le diagnostic de COVID-19 et le décès a été étudié par des courbes de survie calculées selon la méthode de Kaplan-Meier dans chaque groupe défini par la concentration sérique de Cal ($> 1,19$ et $\leq 1,19$ mmol/L) et comparé par log-rank.

Résultats. Dans le modèle de Cox, une association significative a été trouvée entre une concentration sérique de calcium ionisé $> 1,19$ mmol/l et la mortalité à 2 ans, qu'elle soit analysée dans un modèle non ajusté (HR 1,54 [1,04-2,29], $p = 0,032$) ou modèle ajusté (HR = 1,71 [1,12-2,61], $p = 0,014$). Un score GIR ≤ 3 , une dénutrition sévère et un score OSCI ≥ 6 étaient associés à une mortalité à 2 ans dans les deux modèles.

Conclusions. Il existe dans notre étude, une association entre une concentration sérique de calcémie ionisée $> 1,19$ mmol/l et la mortalité à 2 ans d'une infection à Covid-19.

Mots-clés : calcémie, covid-19, personnes âgées.

Association between ionized calcemia and two-year mortality in geriatric patients hospitalized for COVID-19

ABSTRACT

Introduction. Coronavirus disease 2019 (COVID-19) has caused hundreds of thousands of deaths since it was first identified in 2019. Measure of ionized calcium (Ca) are the gold standard, is not routinely measured, as it is a complex process. Hypercalcemia is known to cause diffuse symptoms that can lead to death. The aim of this quantitative, descriptive study is to determine an association between ionized calcium and death two years after Covid-19 infection in geriatric population.

Methods. One hundred and seventy-nine patients hospitalized in the geriatric acute care unit of Angers University Hospital were included in the study. Their data were analyzed between the 1st March 2020 and 29 March 2021. Covid-19 infection was diagnosed by viral PCR or chest CT scan. Ionized calcium levels were determined by potentiometry. Covariates considered were: age, sexe, GIR score ≤ 3 , PTH, CRP, severe undernutrition, history of cancer, history of cardiomyopathy, severe chronic renal failure (defined as clearance < 30 ml/min) and OSCI score. The time elapsed between the diagnosis of COVID-19 and death was studied by survival curves calculated using the Kaplan-Meier method in each group defined by serum Ca concentration (> 1.19 and ≤ 1.19 mmol/L) and compared by log-rank.

Results. In the Cox model, a significant association was found between ionized calcium over 1.19 mmol/l and 2-year mortality, whether analyzed in an unadjusted model (HR 1.54 [1.04-2.29], $p = 0.032$) or adjusted model (HR = 1.71 [1.12-2.61], $p = 0.014$). A GIR score ≤ 3 , severe undernutrition and an OSCI score ≥ 6 were associated with 2-year mortality in both models.

Conclusions. There is an association between Ca and two-year mortality in geriatric patients hospitalized for COVID-19

Keywords: calcemia, COVID-19, older patients.

