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A NEW APPROACH TO ASSESSING CALCIUM STATUS VIA A MACHINE

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ABSTRACT

Background and aims

Calcium plays a fundamental role in biological processes. Ionized calcium (Ca^{2+}), is the biologically active fraction, but in practice total or corrected calcium assays are routinely used to determine calcium status.

Materials and methods

We retrospectively compared total and corrected calcium to assess the calcium status, with ionized calcium which is considered for now like the best indicator. To compensate for their lack of performance we created a machine learning algorithm to predict calcium status.

Results

Corrected calcium performed less well than total calcium with 58% and 74% agreement, respectively, in our population.

Total calcium was especially good for hypocalcemic samples: 93% agreement versus 45% for normocalcemic and 54% for hypercalcemic samples. Corrected calcium was especially good for hypercalcemic and normocalcemic samples: 90% and 84% agreement respectively versus 40% for hypocalcemic samples.

Corrected calcium is mainly faulty in hypoalbuminemia, acid-base disorders, renal insufficiency, hyperphosphatemia, or inflammatory syndrome.

With our ML algorithm, we obtained 81% correct classifications. Its main advantage is that its performance are not influenced by the variables studied or the calcium status.

Conclusion

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In many situations, corrected calcium should not be used. Our ML algorithm may make a better assessment of calcium status than total calcium. Finally, if doubt, an ionized calcium assay should be performed.

1. Introduction

Calcium plays a fundamental role in various biological processes essential to the body and any imbalance (hypo- or hypercalcemia) can have deleterious consequences for patients.

- Total serum or plasma calcium, the most commonly performed quantification assay because it is the easiest to perform, is itself composed of several fractions:
- a non-diffusible fraction (≈ 40%) bound to plasma proteins, mostly to albumin but also to globulins, and others proteins [1], [2], [3].
- a diffusible fraction, not bound to proteins, which breaks down into ionized calcium (≈50% of total calcium) and complexed calcium (≈10% of total calcium is in a complex with anions: bicarbonates, citrates, phosphates, lactates, sulfates…) [1], [2], [4].

Ionized calcium is the biologically active fraction. This fraction is tightly regulated via the calcium sensitive receptor (CaSR) expressed in the parathyroid glands, kidneys and other tissues and two main hormones: parathyroid hormone and 1.25-hydroxyvitamin D [1] thanks to their interventions on three organs, namely, the kidneys, intestine and skeleton.

Ionized calcium is thus considered the best available laboratory test for assessing calcium status of patients but, unfortunately, its determination requires anaerobic sampling generally from an additional syringe, is less stable, partly automated, and higher costs…).

In "healthy" subjects, total calcium equals approximately twice the amount of ionized calcium. However, when there are quantitative abnormalities in serum proteins, and/or abnormalities in the acid-base state, the total Ca-ionized calcium balance is modified and the total calcium assay can no longer be used to deduce the value of ionized calcium and, therefore, calcium status [5], [6].

To overcome this problem, various formulae have appeared, the best known of which are those of Payne, Parfitt and Orrel [2], [7], [8]. With these formulae, corrected calcium can be calculated based on total calcium and total protein concentrations or albumin [2], [6], [7], [8]. Since then, several studies have challenged the use of these "total calcium correction" formulae [5], [9], [10], [11] particularly in patients with renal insufficiency [12], [13], [14], [15], patients with impaired phosphocalcic metabolism like primary hyperparathyroidism or myeloma, [5], [6], [16], [17], patients in intensive care [2], [18], [19], [20] or patients with acid-base imbalances [21], [22].

Correct evaluation of calcium status can improve patient management and reduce costs by avoiding unnecessary and/or inappropriate treatments that may increase the length of stay [23].

In this study, we tried to determine which calcium assay (total or corrected) gave the best reflection of patients' calcium status, taking ionized calcium as the best indicator. We thus compared the

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performances of total and corrected calcium in different situations on a large cohort of adult patients (mainly from intensive care units, resuscitation units or emergency), with different values for albumin, phosphorus, pH, GFR and CRP. In addition, we created a machine learning model to obtain the most reliable prediction of calcium status based on ionized calcium by combining different markers.

2. Materials and methods

2.1. POPULATION UNDER STUDY

We retrospectively studied 7047 patient records (2546 females, 4501 males), aged 15 to 107 years old, admitted to Nîmes University Hospital between December 2017 and April 2021, and for whom arterial pH, ionized Ca, total Ca, albumin, and corrected Ca values were simultaneously available from samples taken at the same time. These are compiled in Supplemental Table 1. For this purpose, anonymous extractions were made from the laboratory computer system (LCS).

Samples were mainly collected from intensive care units (88%) and emergency departments (10%) due to the concomitant availability of the results of all the examinations studied (especially ionized calcium and arterial pH).

Written informed consent was not required for this noninterventional study because the tests noted above were performed as part of routine assessment and no additional tubes were collected for this study, Patients had the ability to refuse, that their biological and clinical data obtained after routine testing completion could be used for research purposes.

2.2. BIOLOGICAL QUANTIFICATION TECHNIQUES USED

Samples were collected in SST BD® tubes for albumin, total calcium, creatinine, CRP, and phosphorus and analyzed on arrival at the laboratory.

For ionized calcium and pH, heparinized whole blood samples were collected in safePICO Radiometer® synringes at the same time as the SST tubes, received in refrigerated bags and analyzed within 15 min of sampling.

This shows the sample collection and testing was especially good.

Albumin, total calcium, CRP, phosphorus, and creatinine were assayed on serum samples on c702 and e801 modules of Roche Cobas analyzers, with Roche diagnostics reagents®.

Phosphorus was determined by the UV Molybdate version 2 technique, RefI: 0.81–1.45 mmol/L, within-laboratory precision (CV): 1% at 1.30 mmol/L and 0.65% at 2.60 mmol/L; and CRP by 4th generation immunoturbidimetry (latex), RefI: <5 mg/L, CV: 1.45% at 9 mg/L and 3% at 50 mg/L. Albumin, total calcium and creatinine were determined by colorimetric techniques. The 2nd generation Bromocresol Green technique was used for albumin, RefI: 40.0–50.0 g/L, CV: 1.8% at

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32 g/L and 1.35% at 48 g/L; 2nd generation NM-BAPTA/EDTA for total calcium, RefI: 2.20–2.60 mmol/L, CV: 0.85% at 2.30 mmol/L and 0.8% at 3.50 mmol/L; enzymatic PAP version 2 plus for creatinine, RefI: 59–104 µmol/L for men, 45–84 µmol/L for women, CV: 2,1% at 90.00 µmol/L and 1.5% at 350 µmol/L.

Ionized calcium determinations and pH measurements were performed on ABL 90 flex® (Radiometer) by potentiometry using a membrane-selective electrode for Ca^{2+}, RefI: 1.15–1.35 mmol/L, CV: 1.38% at 0.36 mmol/L, 0.29% at 0.81 mmol/L, and 0.35% at 1.53 mmol/L and a semiconductor sensor with a PVC membrane sensitive to H^+ ions for pH, RefI: 7.35–7.45, CV: 0.06% at 6.78, 0.02% at 7.17 and 0.05% at 7.53.

The 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate patients' glomerular filtration rate (GFR).

Corrected calcium was calculated using Payne's formula: corrected Ca = total Ca (mmol/L) + [(40 - albumin (g/L))/40].

2.3. STATISTICAL ANALYSIS

R software version 4.1.0 has been used for the statistical analyses. The alpha significant level was set to 5%. In the preliminary analysis, the influence of several factors was investigated (albumin, phosphorus, CKD-EPI etc…) on calcium measurements (total and corrected) and misclassifications (corrected calcium and total calcium vs. ionized calcium). For quantitative variables, Kruskal-Wallis tests were applied to evaluate the differences according to misclassifications (good classification / overestimation / underestimation).

A Principal Component Analysis (PCA) was performed (Supplemental Fig. 1) with several variables (total Ca, albumin, phosphorus etc…) to look for links between these variables and ionized calcium in a multivariate way (3 classes: hypocalcemic / normocalcemic /hypercalcemic).

To best mimic the ionized calcium, machine learning algorithms were tested to combine several variables with total calcium. Both supervised classification (Ordinal logistic regression, Ordinal Random Forest, Adjacent Categories Probability Model for Ordinal Data, CART on Ordinal Responses and Support Vector Machines) and regression (Multiple linear regression, Random Forest regression and SVM Regression) were tested.

In the final model, the variables were selected according to performance as well as their availability and ease of use in current practice. The R package caret (short for Classification And Regression Training) was used to train the models.

In this study, the composition of the class variable of interest (ionized calcium) is clearly unbalanced with sample sizes 3851, 2801 and 395 for respectively Hypocalcemic, Normocalcemic and hypercalcemic. Given that the predictions have to be good in all categories (without preference), the training set need to have balanced group sizes otherwise the group of hypercalcemic would be neglected. Concretely, in this study, the training and test sets have been built in the following way:

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- Only the samples with no missing data for variables ionized calcium, total calcium, albumin, Phosphore and Age were kept leading to group sizes 3598, 2580 and 375 for respectively Hypocalcemic, Normocalcemic and hypercalcemic.
- 500 samples have been randomly selected for both Hypocalcemic and Normocalcemic categories.
- For the Hypercalcemic group, an oversampling strategy has been used. 248 samples have been randomly selected (~2/3 of the total size of this group). Then, 252 sampling with replacement have been processed among this 248 samples in order to reach the total size of 500 samples.
- All the remaining samples (respectively 3098, 2080 and 127) were put into the test set used for the performance evaluation.

The explanatory variables were centered and scaled prior to the training process. The parameters of the different algorithms have been tuned with "train" function of caret package, the best parameters were selected according to accuracy (good classification rate) for classification algorithm and RMSE (Residual Mean squared error) for regression algorithms. Then, the continuous results obtained with regression models were followed by an ordered logistic regression in order to obtain class predictions.

Finally the best model was chosen based on its diagnostic performances on the test set. For this particular 3-class diagnostic problem, the performances have been evaluated as follows:

- Global accuracy (the proportion of correct classifications regardless of group).
- By analogy to sensitivity in the binary case, we defined "sensitivity-hypo", "sensitivity-normal" and "sensitivity-hyper" for each class, i.e. the proportion of correctly identified hypocalcemic, normocalcemic and hypercalcemic patients.
- By analogy to positive predictive value (PPV) in the binary case, we defined "PPV-hypo", "PPV-normal" and "PPV-hyper" for each class, i.e. the probability of being truly hypocalcemic, normocalcemic and hypercalcemic given that the test had diagnose it.

Based on all these criteria, the final model selected was the Random Forest regression. It allows in one hand to predict the quantitative value of ionized calcium and in the other hand the different classes thanks to the ordered logistic regression model. This second step is also useful because it provides a reliability index that could be useful for the interpretation of results. This index is in [0,1] range, we can trust the prediction with high level of confidence when the index is high (e.g. >0.7) whereas we can have some doubts when this index is lower.

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3. Results

3.1. BIOLOGICAL CHARACTERISTICS OF THE PATIENT POPULATION

The biological characteristics of the patient population under study are summarized in Supplemental Table 1. The mean and median ionized calcium of our patients were 1.14 mmol/L, RefI: 1.15 to 1.35 mmol/L, indicating a tendency towards hypocalcemia.

3.2. ABILITY OF TOTAL CA, CORRECTED CA AND THE ML ALGORITHM TO DETERMINE OUR PATIENTS' CALCIUM STATUS

Total calcium classifies patients well in 74% (Table 1) of cases, which is in line with what was observed by Grzych et al. on patients hospitalized at Lille University Hospital [22] and, above all, it classifies hypocalcemic patients very well: 94% agreement compared with 46% for normocalcemic patients and 54% for hypercalcemic patients.

Table 1. Performance of total calcium (total Ca), corrected calcium (corrected Ca) and algorithm (ML algorithm for machine learning algorithm) to predict calcium status. Accuracy-global = overall agreement, Sensitivity-hypo = agreement in the event of hypocalcemia, Sensitivity-normal = agreement in the event of normocalcemia, Sensitivity-hyper = agreement in the event of hypercalcemia, PPV-hypo, PPV-normal, and PPV-hyper = positive predictive value of hypo/normo/hypercalcemia respectively.

	Accuracy-global	**Sensitivity-hypo**	**Sensitivity-normal**	**Sensitivity-hyper**	**PPV-hypo**	**PPV-normal**	**PPV-hyper**
Total Ca	0.74	0.94	0.46	0.54	0.72	0.79	0.83
Corrected Ca	0.58	0.40	0.84	0.90	0.89	0.48	0.37
ML algorithm	0.78	0.77	0.77	0.88	0.86	0.69	0.60
ML algorithm with confidence index of >70%	0.81	0.81	0.80	0.90	0.88	0.74	0.65

Corrected calcium ranks patients well in 58% of cases and, in particular, ranks hypercalcemic and normocalcemic patients very well: 90% and 84% agreement respectively versus 40% for hypocalcemic patients.

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Given the absence of a reliable, easily accessible marker for calcium status in all situations encountered in the hospital, we created a machine learning model.

The model we selected combines the following predictors: total blood calcium (mmol/L), blood albumin (g/L), blood phosphorus (mmol/L) and age (years) in order to obtain a continuous score that provides the most accurate approach to ionized calcium and, therefore, true calcium status. Taking the ionized calcium level as a reference, the overall percentage of correct classifications was 78%. Each calcium status (hypocalcemic, normocalcemic or hypercalcemic) was correctly identified with a probability greater than 75%.

Moreover, the result given by the ML algorithm is accompanied by a confidence index. In our study, we chose a threshold of 70% to improve the reliability of the prediction by not "rejecting" too many samples; in this situation, the overall concordance rate is 81% (Table 1), each calcium status is correctly identified with a probability of 80% or over. 13% of the samples had a ≤70% confidence index, a situation in which the performance of ionized calcium therefore seems more appropriate. If we increase the threshold of confidence, we gain in performance but obtain more rejections (Supplemental Table n°2).

3.2.1. IMPACT OF ALBUMINEMIA ON DETERMINING CALCIUM STATUS

Since albumin is the major calcium-binding protein and must be measured to calculate corrected calcium via Payne's formula (and other formulae for correcting calcium), we studied its impact on determining the calcium status via total calcium, corrected calcium and the ML algorithm.

In Fig. 1A, corrected calcium performs worse overall than total calcium which, in turn, performs worse than the ML algorithm created to determine calcium status.

Indeed, in Fig. 1A we can observe a clear drop in the performance of corrected calcium when albumin is lower than 30 g/L. Our population above 50 g/L is too small to conclude. The performance of the ML algorithm and of total calcium is less affected by albumin variation.

We also noticed that the curves for the overestimation (1B) and underestimation (1C) of total calcium and corrected calcium cross at around 40 g/L of albumin. Corrected calcium below 40 g/L increasingly overestimates calcium status as albumin decreases. Conversely, above 40 g/L it increasingly underestimates it as the albumin increases. The opposite trends are observed for total calcium: underestimation below 40 g/L, overestimation above.

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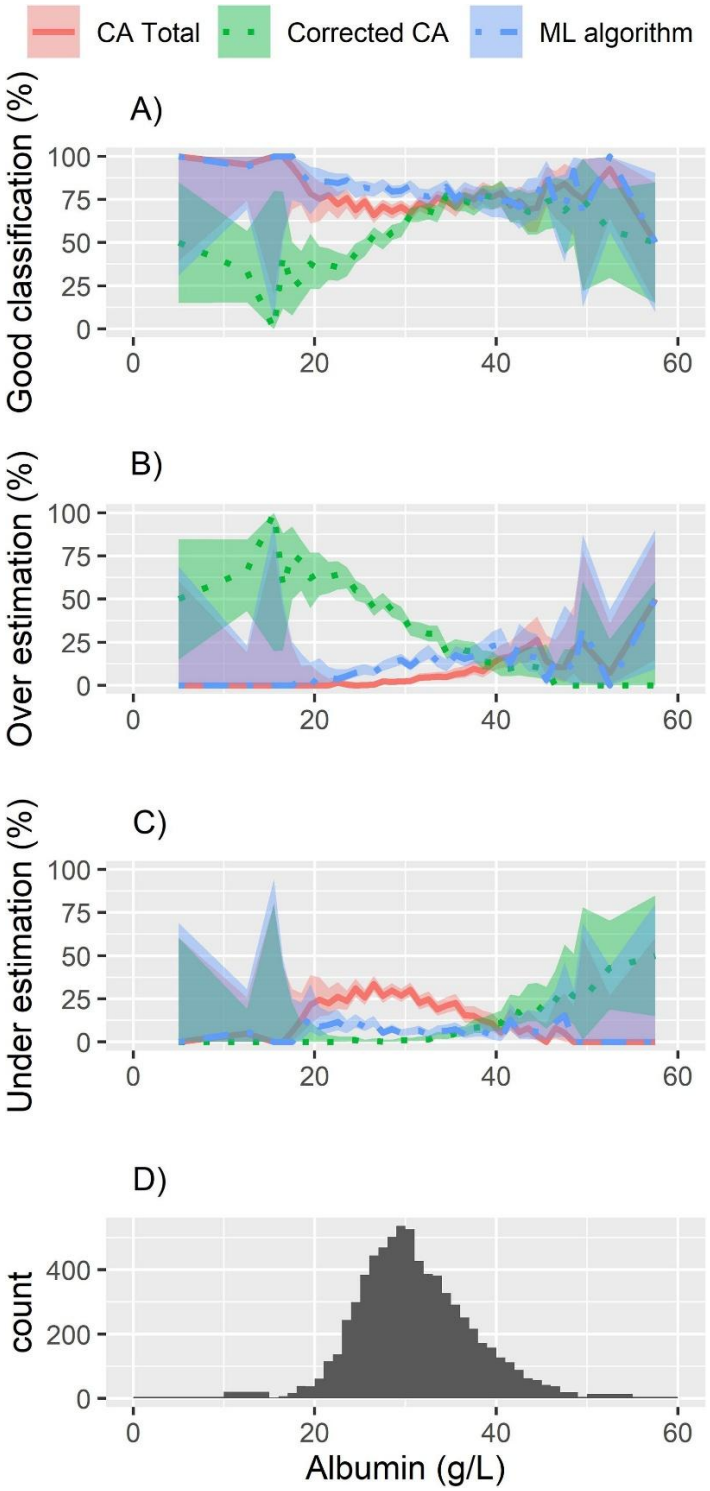

Fig. 1. Performances of total calcium, corrected calcium and the ML algorithm to predict calcium status determined by ionized calcium (best available test) based on albumin (g/L). 95% confidence bands based on the number of patients. (A) Good classification is the rate of good classification obtained by each approach (total calcium, corrected calcium, and the ML algorithm) as a function of the variation of a third variable, here albumin. The overestimation curve (B) and underestimation curve (C) indicate in which direction and in what proportion each approach is wrong according to the third variable. (D) Size of the study population based on albumin (g/L).

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3.2.2. IMPACT OF PHOSPHATEMIA ON DETERMINING CALCIUM STATUS

Phosphates can be in a complex with calcium and, like calcium, are regulated by PTH and 1.25-OH-vitamin D, so we also studied the impact of its concentration on determining calcium status by total calcium, corrected calcium and the ML algorithm.

Fig. 2A shows that, as the value of phosphorus increases, the ML algorithm and, above all, total calcium perform better in predicting calcium status. It can be seen that the underestimation curve (2C) by total calcium decreases with the increase of phosphorus. Corrected calcium is less impacted by phosphatemia. The performance of the ML algorithm is at least equivalent to that of total calcium over the entire measurement range studied and the ML algorithm performs better when phosphatemia is normal, which was the case for the majority of our patients.

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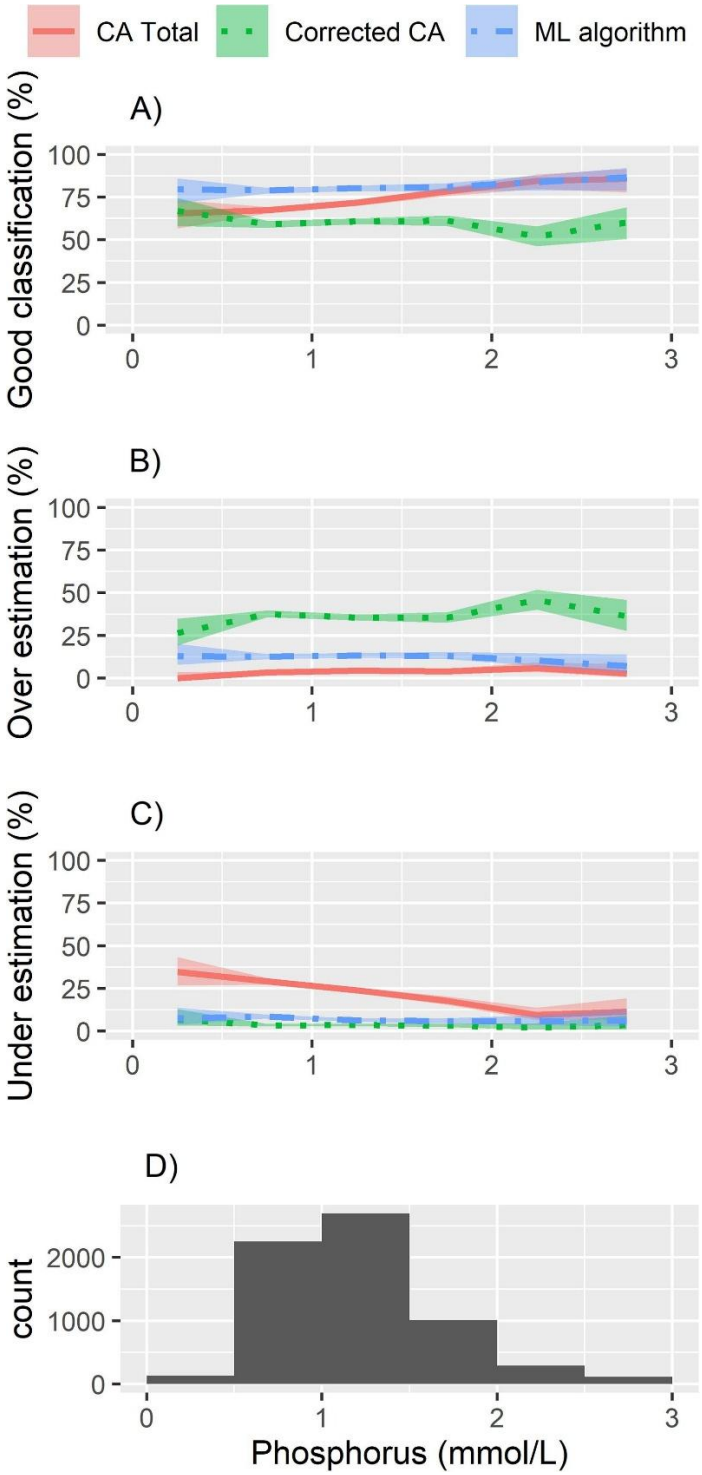

Fig. 2. Performances of total calcium, corrected calcium and the ML algorithm for predicting calcium status determined by ionized calcium (best available test) as a function of phosphatemia (mmol/L). 95% confidence bands based on the number of patients. (A) Good classification is the rate of good classification obtained by each approach (total calcium, corrected calcium, and the ML algorithm) according to the variation of a third variable, in this case, phosphatemia. The overestimation curve (B) and underestimation curve (C) indicate in which direction and in what proportion each approach is wrong according to the third variable. (D) Size of the study population as a function of phosphatemia (mmol/L).

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3.2.3. IMPACT OF ACID-BASE BALANCE ON DETERMINING CALCIUM STATUS

Since acid-base balance is an important determinant of calcium binding to proteins (competition between H^+ protons and calcium towards proteins [6]) we wanted to study its impact on determining calcium status by total calcium, corrected calcium and the ML algorithm.

In Fig. 3, we see again that corrected calcium performs worse overall than total calcium which, in turn, performs worse than the ML algorithm in determining calcium status (3A). Corrected calcium is especially less efficient in conditions of severe alkalosis and acidosis. Indeed, a U-shaped overestimation curve (3B) is observed with the corrected calcium: the further the pH is from physiological values, the more the corrected calcium overestimates the calcium status.

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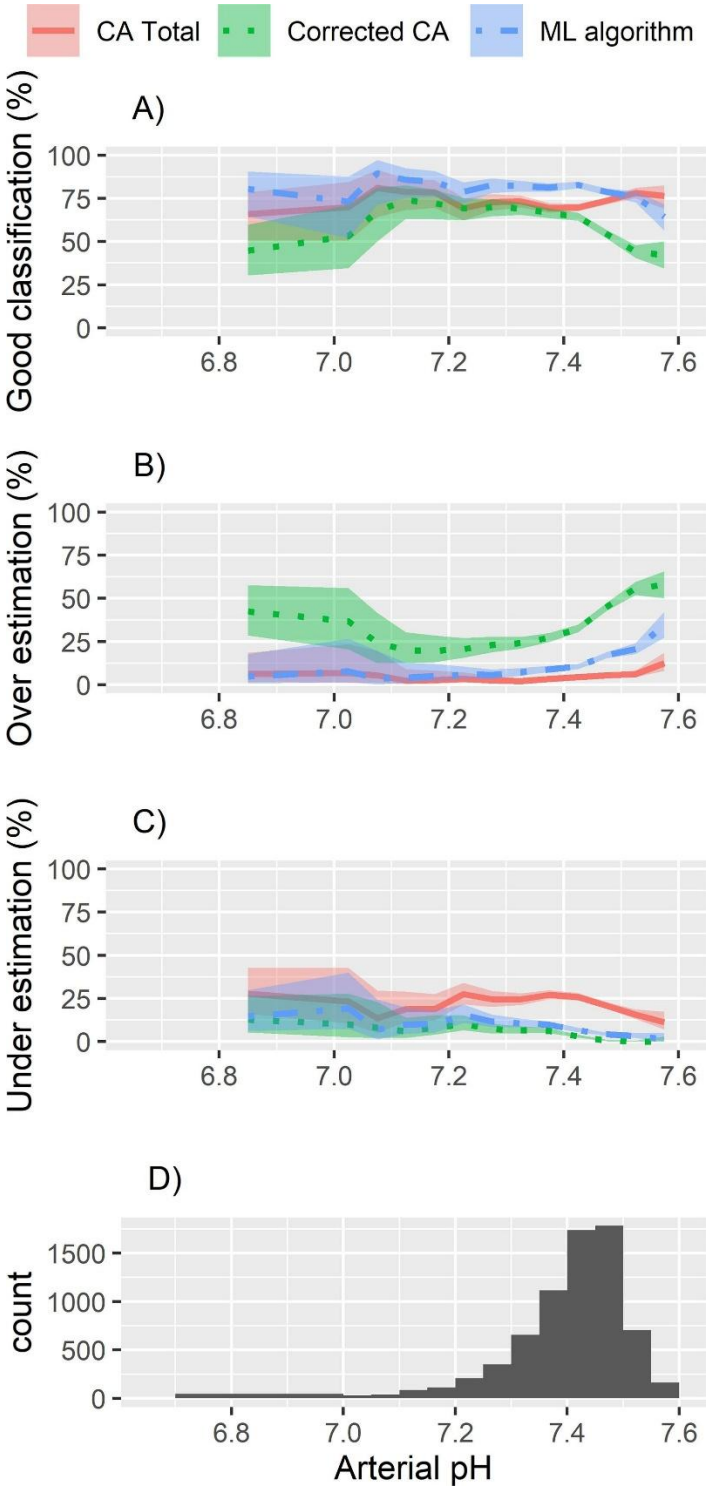

Fig. 3. Performances of total calcium, corrected calcium and the ML algorithm to predict calcium status determined by ionized calcium (best available test) according to arterial pH. 95% confidence bands based on the number of patients. (A) Good classification is the rate of good classification obtained by each of the approaches (total calcium, corrected calcium, and ML algorithm) according to the variation of a third variable, here arterial pH. The overestimation curve (B) and underestimation curve (C) indicate in which direction and in what proportion each approach is wrong according to the third variable. (D) Size of the study population according to arterial pH.

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3.2.4. IMPACT OF RENAL FUNCTION ON DETERMINING CALCIUM STATUS

As mineral and bone metabolism disorders are associated with chronic kidney disease, like other teams [12], [13], [14], [15] we also investigated the impact of GFR on determining calcium status by total calcium, corrected calcium, and the ML algorithm.

The greater the decrease in GFR, the better total calcium was at predicting calcium status. Indeed, in Fig. 4, the percentage of underestimation decreases as renal failure progresses (4C). The performance of the ML algorithm appears to be somewhat less impacted by GFR and is a better indicator of calcium status than total calcium, which itself is better than or equivalent to corrected calcium (4A).

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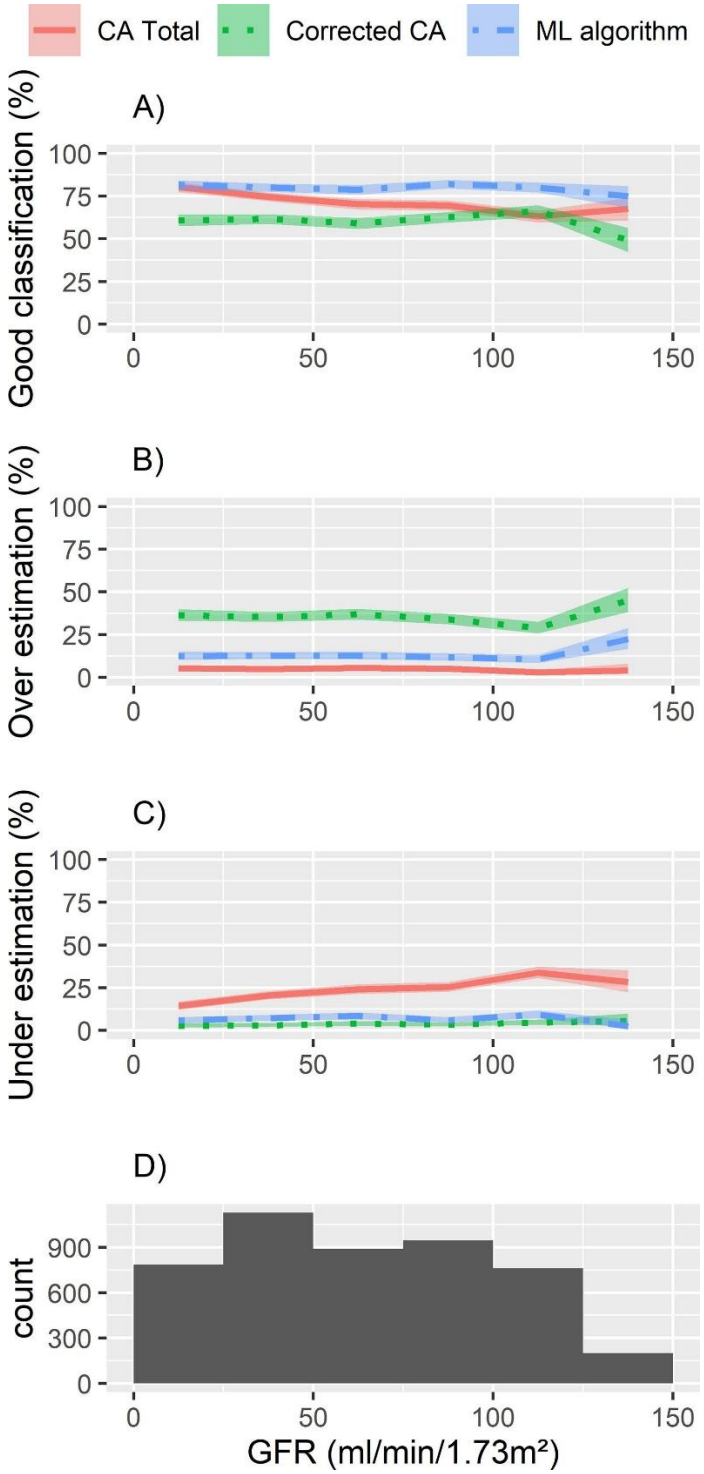

Fig. 4. Performances of total calcium, corrected calcium and the ML algorithm to predict calcium status determined by ionized calcium (best available test) according to the GFR calculated by the CKD-EPI equation in mL/min/1.73 m^2. 95% confidence bands based on the number of patients. (A) Good classification is the rate of good classification obtained by each of the approaches (total calcium, corrected calcium, and ML algorithm) according to the variation of a third variable, in this case, GFR (mL/min/1.73 m^2). The overestimation curve (B) and underestimation curve (C) indicate in which direction and in what proportion each approach is wrong according to the third variable. (D) Size of the study population according to the GFR (mL/min/1.73 m^2).

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3.2.5. IMPACT OF INFLAMMATION ON DETERMINING CALCIUM STATUS

During an inflammatory syndrome, especially if it is chronic, the distribution of blood proteins being modified, we studied the impact of inflammatory syndrome measured by CRP on determining calcium status by total calcium, corrected calcium and the ML algorithm.

Again, in Fig. 5, the ML algorithm performs better than total calcium, which underestimates calcium status in about 25% of cases regardless of CRP value. Corrected calcium is the least efficient: it overestimates the calcium status in over 30% of cases as soon as the CRP is above 50 mg/L (5B). Above 350 mg/L, the number of patients in our population is too small (n = 112) to reach a reliable conclusion.

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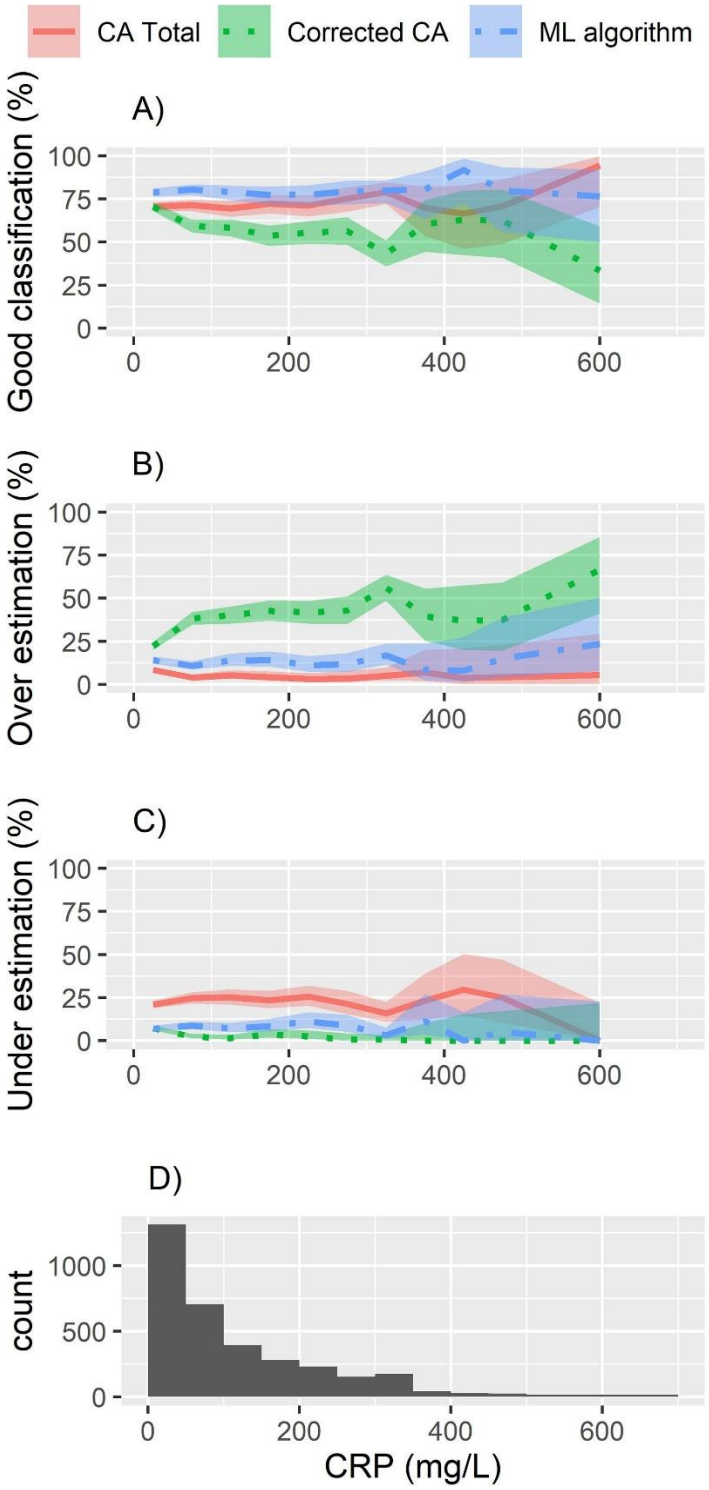

Fig. 5. Performances of total calcium, corrected calcium and the ML algorithm to predict calcium status determined by ionized calcium (best available test) based on CRP (mg/L). 95% confidence bands based on the number of patients. (A) Good classification is the rate of good classification obtained by each of the approaches (total calcium, corrected calcium, and ML algorithm) according to the variation of a third variable, in this case, CRP (mg/L). The overestimation curve (B) and underestimation curve (C) indicate in which direction and in what proportion each approach is wrong according to the third variable. (D) Size of the study population based on CRP (mg/L).

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4. Discussion

In the general population, the prevalence of dyscalcemia of all etiologies is around 1 to 3% [24]. Our study was carried out in hospitals, mainly in intensive care units, where the prevalence of dyscalcemia reached 60%. Indeed 54.7% of the samples showed hypocalcemia and 5.6% hypercalcemia. The increase in the prevalence of dyscalcemia in the population we studied is explained by the many complex pathologies suffered by patients in continuing care, which favor an imbalance in the phosphocalcic metabolism. Steele et al. [19] also reported 55.2% of hypocalcemic patients on admission to the ICU.

The aim of our study was to determine which calcium assay (total or corrected) was the best indicator of the patients' calcium status, ionized calcium being the best available test even if some studies suggest that correcting an obnormal ionized calcium may not be clinically appropriate [11]. Thus, we compared the performance of total and corrected calcium in different situations: according to albuminemia, phosphatemia, arterial pH, GFR (CKD-EPI), and CRP.

Although the formulae for correcting calcium levels had been "developed" for dysproteinemia, we, like others, observed that corrected calcium was mainly faulty in hypoalbuminemia [21], [25], especially when albumin was below 30 g/L. However, it is important to bear in mind the significant variability of results depending on the type of albumin assay technique [26], [27]. Other teams used different techniques from ours to determine albumin: for Smith et al. it was the bromcresol purple method [25] which generally gives lower results in patients with renal failure [28] and therefore higher corrected calcium than our bromcresol green method (the most widely used technique in France in 2022). However, we obtained the same conclusions and same threshold of 30 g/L albumin, maybe because the population they were studying did not consist mainly of patients with renal failure. Pekar et al. [21] used an immunoturbidimetric technique which also gave lower values but obtained a threshold of 35 g/L.

In Fig. 1B and 1C we can also see that the over- and underestimation curves for total calcium and corrected calcium intersect at around 40 g/L albumin. Corrected calcium below 40 g/L increasingly overestimates calcium status as albumin decreases. Conversely, above 40 g/L it increasingly underestimates it with increasing albumin. The opposite trends are observed for total calcium: underestimation below 40 g/L, overestimation above. This can probably be explained by the formula used to calculate corrected calcium: corrected Ca = total Ca (mmol/L) + [(40 - albumin (g/L))/40] because, if another reference value is used in the formula, the curves cross at that value (Supplemental Fig. 2).

In most studies, data obtained in patients with acid-base disorders are excluded [15], [25] as the Payne formula has not been validated in this context. We chose to study data from patients with alkalosis and acidosis, the overestimation curve for corrected calcium describes a U-shaped curve: indeed, as in Pekar et al.'s and Grzych et al.'s studies [21], [22], we noted poor agreement between corrected calcium and ionized calcium in alkalosis. In our study, we also observed poor agreement in cases of severe acidosis whereas Slomp et al. did not observe any impact from pH [18]. We therefore confirm that Payne's formula in unsuitable for use in acid-base disorders.

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We also investigated the agreement between corrected calcium, total calcium and ionized calcium according to GFR. In our investigation of GFR, Fig. 4 shows that total calcium performs better than corrected calcium by underestimating less and less calcium status as GFR decreases. This observation is in agreement with the literature as other teams before us had already concluded that corrected calcium should not be taken into account in renal failure patients [12], [15], [25]. This is important because calcium status is a parameter that should be monitored by nephrologists for the management of mineral and bone metabolism disorders according to the KDIGO 2017 recommendations and to recent studies in dialysis patients showing that poor evaluation of calcium status may lead to a greater risk of mortality, particularly due to cardiovascular disease [29], [30].

Inflammatory conditions also appear to decrease the ability of corrected calcium to assess calcium status. Perhaps this observation is related to the lower albumin concentrations observed in chronic inflammatory states or to an interference on the albumin determination by the bromcresol green method in this context, as suggested by Godefroy et al. [27]. Other investigations with other albumin quantification techniques must be performed to reach a conclusion.

Globally, we observed a trend towards overestimation of blood calcium levels by corrected calcium. This observation is in agreement with the study by Zulkulfi et al. in intensive care patients [20], and also the study by Law et al. [15] and Pekar et al. [21] despite the fact that they used 3 different albumin assay techniques.

To take into account the impact of the variables previously studied, other formulae have been tested, some integrating anions, pH, phosphorus, etc., but none are capable of reflecting the complexity of calcium homeostasis [11], [31], [32]. This is why we tried to create a model from machine learning algorithms to obtain a continuous score as close as possible to ionized calcium.

With our ML algorithm and a confidence index >70%, we obtained 81% overall agreement between Ca2+ and the model (Table 1) without additional sampling, tubing, or equipment.

In our population, this model greatly improves the detection of hypercalcemia and normocalcemia compared with total calcium. Compared with corrected calcium, it is especially more efficient in detecting hypocalcemia. On the other hand, the concordance rate is stable, the percentage of correct classifications is greater than or equal to 80% in all the circumstances studied, which is an advantage compared with total calcium and especially with corrected calcium which are highly dependent on the clinico-biological characteristics of the population under study.

Finally, the associated confidence index lets us know whether it is necessary to do an ionized calcium assay or if we can trust it. In our study, we retained a threshold of 70% to obtain at least 80% of good classifications whatever the calcium status.

5. Conclusions

The conclusions of our study are limited by the particular nature of the population we studied. Indeed, 88% of patients came from intensive care units, for reasons of availability of biological data.

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The next stage will be to confirm these observations and test our ML algorithm on a population of healthy controls in a prospective study.

Clinicians and biologists are aware of the need to assess calcium status in a simple and reliable way, but also of the limits of total calcium and corrected calcium in various pathological situations often encountered in hospital.

At present, none of the available indicators for calcium status are perfect (Table 1): total calcium identifies hypocalcemia very well but hypercalcemia and normocalcemia much less well, whereas corrected calcium identifies hypercalcemia and normocalcemia very well but hypocalcemia much less well. Moreover, the latter should not be used in cases of hypoalbuminemia (<30 g/L), acid-base disorders, renal insufficiency, hyperphosphatemia, or inflammatory syndrome (Supplemental Table 3). Its use in hospitals, especially in critical care patients, is therefore irrelevant whereas, in an ambulatory setting, it should be interpreted considering the parameters previously mentioned. Finally, ionized calcium, considered as the best indicator of Ca status, is less accessible in routine use as it is subject to pre-analytical constraints, analytical constraints, and economic constraints. It should therefore be reserved for special cases.

A new alternative might be to use our ML algorithm which, without additional analysis, gives results that tie in with the results of ionized calcium in 81% of cases (Table 1). Moreover, its performance is not affected by the pathological situations frequently encountered in hospitals: hypoalbuminemia, acid-base disorders, renal insufficiency, phosphatemia and inflammation.

CRediT authorship contribution statement

Candice Bancal: Conceptualization, Methodology, Validation, Writing – original draft. **Florian Salipante:** Software, Formal analysis, Visualization, Writing – original draft. **Nassim Hannas:** Data curation, Writing – review & editing. **Serge Lumbroso:** Supervision, Writing – review & editing. **Etienne Cavalier:** Writing – review & editing. **David-Paul De Brauwere:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.cca.2022.12.018.

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