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# Determinants of Total/ionized Calcium in patients undergoing citrate CVVH: A retrospective observational study

Willem Boer[a],*, Mathias van Tornout[a], Francesca Solmi[c], Xavier Willaert[a], Miet Schetz[b], Heleen Oudemans-van Straaten[d]

[a] Department of Anesthesiology, Intensive Care Medicine, Emergency Medicine & Pain Medicine, Ziekenhuis Oost Limburg ZOL, Genk, Belgium
[b] Department of Laboratory and Intensive Care Medicine, Catholic University Leuven, Belgium
[c] Data Science Institute, Interuniversity Institute for Biostatistics and statistical Bioinformatics, Hasselt University, Hasselt, Belgium
[d] Amsterdam University Medical Centre, location VUmc, the Netherlands
*Corresponding author : willem.boer@zol.be

## Abstract

*Purpose*: To identify potential determinants of the Total/ionized Ca ratio (T/iCa), a marker of citrate accumulation.
*Materials and methods*: Single-center retrospective observational study evaluating citrate dose, citrate target, albumin, phosphate, pH, lactate, and APACHE II score as potential determinants. Linear mixed models (LMM) using citrate dose and citrate target were developed describing associations with T/iCa.
*Results*: From a dataset of 471 samples in 103 patients, an LMM in 379 complete samples (95 patients) sets revealed that citrate dose, pH, phosphate, albumin and APACHE were interactively related to T/iCa. A rising citrate dose was associated with a higher increase in T/iCa when phosphate was high, and less when phosphate was low. A rising albumin was associated with a higher increase in T/iCa when APACHE was high and phosphate was low and less when APACHE was low and phosphate high. In case of acidosis, a rising lactate was associated with a higher increase in T/iCa.
In the LMM using citrate target, citrate target and pH were the main independent predictors of T/iCa with albumin, phosphate and APACHE score as modifiers.
*Conclusions*: Besides citrate dose, a high pH and high phosphate, albumin and APACHE are also associated with a rising T/iCa.

Abbreviations: CVVH, continuous venovenous hemofiltration; T/iCa, total versus ionized calcium ratio; LMM, linear mixed model; CRRT, continuous renal replacement therapy.

## 1. Introduction

Citrate accumulation is a feared complication of citrate anticoagulation which has become the preferred choice for anticoagulation in continuous renal replacement therapy (CRRT) [1]. Citrate induces anticoagulation by reversible binding (chelation) of calcium, causing extracorporeal hypocalcemia. Since calcium is a necessary cofactor in the coagulation cascade, clotting is prevented. Before re-entrance of circuit blood to the patient, the calcium concentration is restored. Regional anticoagulation is the result. Although citrate anticoagulation reduces bleeding and prolongs circuit life span [2], appropriate monitoring of its most important complication, citrate accumulation, remains a point of concern. Citrate accumulates when its metabolism is impaired [3]. This results in metabolic acidosis and systemic hypocalcemia, causing hypotension due to myocardial depression and vasodilation. Typical risk factors

in ICU patients are shock and a failing liver [1]. At present, a bedside measurement of citrate concentration is not available. An increased ratio of total versus ionized Calcium (Total/ionized Ca (T/iCa)) is generally used as an indirect marker for citrate accumulation. When citrate metabolism is impaired, Ca is not released from the citrate-calcium complexes, decreasing ionized Ca. Total Ca (including the citrate-bound calcium) further increases if the resulting decrease in ionized calcium is compensated by extra calcium administration.

The relationship between T/iCa and citrate concentration has been described in a number of studies [[4], [5], [6]]. However, other factors than the citrate dose may influence the T/iCa ratio, such as albumin [7,8], phosphate [9,10], lactate [11], pH [12,13] and severity of disease which, if high, can increase circulating unmeasured anions [[14], [15], [16]]. None of these studies evaluated the association between the T/iCa ratio and the combination of these factors. The objective of this study is to identify the factors associated with the T/iCa in patients undergoing citrate CVVH.

## 2. Material and methods

A single center retrospective observational study was performed in the mixed medical-surgical ICU of Ziekenhuis Oost Limburg, Genk, Belgium, a large non-University teaching hospital. All consecutive adult patients undergoing continuous venovenous hemofiltration (CVVH) using citrate as anticoagulant were included. Patients already receiving renal replacement therapy at the time of admission to ICU were excluded. According to protocol, citrate was not used in patients with suspected liver failure. The study protocol was approved by the local institutional review board (Commissie Medische Ethiek Ziekenhuis Oost-Limburg, approval no. 16/053 U). The need for informed consent was waived because the study analyzed variables collected during standard medical care. A proportion of patients was also included in a prospective, randomized study (NCT 02194569) designed to elucidate the effects of citrate CVVH on magnesium and calcium balance (see below).

### *2.1. CVVH procedure*

Citrate CVVH was performed using the Prismaflex® (Baxter international inc. Deerfield IL, USA; formerly Gambro lundia AB, Lund, Sweden) and a 1,5m2 AN69 HF dialyzer (Kuf 37 mL/h/ mmHg). Vascular access was established by ultrasonography-guided placement of a 12 F hemodialysis catheter in either jugular, femoral or subclavian vein (in order of preference) and blood flow rate was set according to body weight (range 120–180 mL/min) (see table appendix 1). As part of the set-up procedure of the Prismaflex®, haematocrit and weight were entered to correct calculated plasma volume. Citrate was administered pre-filter in the form of Prismocitrate 18/0®, containing 18 mmol of citrate per liter as well as sodium (140 meq/L) and chloride (86 meq/L). In this setting, mean filtration fraction is about 38% assuming a fluid removal rate of 50 mL/h. The Prismaflex software includes an algorithm allowing the clinician to individualize the level of anticoagulation in the circuit by setting the ‘citrate target’, defined as the citrate concentration in mmol/L in the circuit blood. At CVVH initiation the ‘citrate target’ was routinely

set at 3.0 mmol/L and subsequently adjusted to keep post-filter iCa values within the range of 0.25–0.35 mmol/L (1.0 to 1.4 mg/dL). In the patients included in the balance study (see above), initial citrate targets were randomly set at 2.5 or 4.5 mmol/L and adjusted to achieve a post-filter iCa of 0.33–0.40 mmol/L (1.3–1.6 mg/dL) or 0.2–0.28 mmol/L (0.8–1.1 mg/dL) respectively. Inclusion of patients from this study provided a broader range of citrate targets (and therefore citrate concentrations in the circuit) increasing the value of the database. Prismaflex® compensates the extracorporeal loss of calcium bound in calcium-citrate complexes using a standardized closed-loop system for the dosing of calcium post-filter (Ca-chloride 550 mmol/L). Calcium administration was routinely set at 100%. Net fluid removal rates were targeted according to individual needs. Post-filter substitution fluid (prismOcal B22®) (composition in appendix 2) was administered to achieve an effluent flow rate of 30mL/kg/h (fluid amounts contributed by pre-filter Prismocitrate 18/0®, post-filter substitution fluid (prismOcal B22®) and patient fluid removal rates, corrected as if delivered in a post dilution mode and normalized to patient body weight).

Neither prismocitrate 18/0® nor prismOcal B22® contain phosphate, which was supplemented separately, targeting normal values (0.87–1.45 mmol/L in our laboratory).

To guarantee adequate clearance, circuits were disconnected when transmembrane pressure increased and filters were not used beyond 72 h.

### *2.2. Study measurements*

Arterial blood was sampled from a separate arterial catheter to determine pH, albumin, phosphate, total Ca, iCa and lactate. The following variables were also collected: gender, age, admission diagnosis, APACHE II on ICU admission and before start of CVVH, KDIGO criteria for AKI at CVVH initiation and shock requiring vasopressor or inotropic medication. Blood samples were taken simultaneously at 6 a.m. The citrate target (in mmol/L) was noted and the amount of citrate administered (in mmol/kg/h), the citrate dose, was calculated by dividing the amount of citrate administered (prismocitrate 18/0®) in mmol/h by bodyweight (in kg).

### *2.3. Definitions*

A total to ionized calcium (T/iCa) ratio of ≥2.4 was considered a risk for citrate accumulation.

### *2.4. Endpoints of study*

Study endpoints were the individual and combined associations of citrate dose, citrate target and albumin, phosphate, pH, lactate, with the T/iCa ratio all at the same time point. APACHE II score at initiation of CVVH, was also incorporated as explaining factor.

### *2.5. Statistical analysis*

Normally distributed values are reported as mean ± standard deviation, not-normally distributed values as median with 25th to 75th percentile (interquartile range). Normality was determined by the Shapiro-Wilks test.

General associations between T/iCa and the explanatory variables citrate dose, albumin, phosphate, pH, lactate and APACHE II at start of CVVH, were determined by using the linear mixed model (LMM) methodology, allowing for the correct handling of repeated measures in the same patient. The data rows with at least one missing value were deleted from the analysis, assuming that the reason for their absence was not related to either the unobserved value or to the other parameters. The model was built with T/iCa as response variable, patient as random intercept and other measured parameters as fixed effects. The patient as random intercept assumes that a similar association between T/iCa and the other parameters holds for all CVVH patients and that the observations from the same patients are related to each other. Linear fixed associations were studied, as were all possible two-way interactions. During model selection, non-significant interactions were dropped, resulting in the model fit reported.

Two Linear Mixed models were developed, using the citrate dose as surrogate for the citrate concentration in the circuit (citrate dose administered to the circuit per hour corrected for body weight, in mmol/kg/h) or using the citrate target (citrate concentration in circuit blood in mmol/L, the citrate setting on the Prismaflex®) because this variable is visible in clinical practice.

To compare patients with and without a risk for citrate accumulation (cut off T/iCa ≥ 2.4), unpaired Student t-test or the Mann-Whitney U test was used as appropriate. To allow for the correct handling of repeated measures in the same patient (in case of citrate, albumin, phosphate, pH and lactate), a linear mixed model with the indicator T/iCa ≥2.4 as covariate, a patient random effect and each of the parameters as response variables was used. For some parameters, a transformation of the response was needed. A p-value of less than 0.05 was considered statistically significant.

## 3. Results

Between January 2013 and June 2016, a total of 471 blood samples sets were collected, in 103 patients (Fig.1).
These patients underwent citrate CVVH for a total of 20,963 h, a median of 160 (97–263) hours per patient. Baseline characteristics including admission diagnoses are described in Table 1. Median age was 69 (63–76) years, median APACHE II score at initiation of CVVH was 26 (22−32) and 88% of patients depended on vasopressor or inotropic therapy at CVVH initiation.

Study parameters are summarized in Table 2. Median T/iCa of all values studied was 2.1 (2.01–2.20). The median citrate target was 3.8 (3.5–4.0) mmol/L, mean citrate dose was 0.37 mmol/kg/h (0.33–0.42),

mean albumin was 29.2 (± 5.04) g/L, median phosphate was 0.88 (0.69–1.14) mmol/L, median pH was 7.44 (7.39–7.48) and median lactate was 1.3 (1.00–1.98) mmol/L.

### *3.1. Linear mixed model (LMM) for T/iCa using citrate dose*

A total of 379 complete sample sets, in 95 patients, were included. Citrate dose, phosphate, albumin, pH, lactate and APACHE were related to T/iCa in a complex interactive way. There was a significant linear association between T/iCa and the two-way interactions citrate dose*phosphate, albumin*phosphate, albumin*APACHE II ($p < .001$) and pH*lactate ($p < .05$) (Fig. 2). According to this model, a rising citrate dose was associated with a higher increase in T/iCa ratio when phosphate was high, and less so when phosphate was low (see Fig. 2A). A rising albumin was associated with a higher increase in T/iCa ratio when APACHE was high and phosphate was low and less so when APACHE was low and phosphate high (see Fig. 2B). Finally, a rising lactate was associated with a higher increase in T/iCa ratio when pH was low (see Fig. 2C). Data for high lactate when pH was high were limited.

Both LMMs are portrayed in full in Appendix 3. Study parameters of this LMM sample set are summarized in Appendix 4, comparison of samples with T/iCa < 2.4 and ≧2.4 in Appendix 5.

### *3.2. Linear mixed model (LMM) for T/iCa using citrate target*

A total of 372 complete sample sets, in 95 patients, were included in this linear mixed model. In this LMM, three single variables, citrate target, pH and lactate, each showed a significant linear association with T/iCa. A 2 mmol/L increase in citrate target, a 0.17 increase in pH, and an increase as high as 8 mmol/L in lactate was needed to increase the T/iCa ratio by 0.1. Both LMMs are portrayed in full in appendix 3.

The estimated associations between T/iCa and citrate target, pH and lactate are presented in scatter plots setting the other parameters at the average levels observed in the data set (Fig. 3).

In addition, there was a significant linear association between T/iCa and the two-way interactions albumin*phosphate and albumin*APACHE II, similar to the association found in the LMM using citrate dose.

### *3.3. Comparison of normal vs. high T/iCa samples in all sample sets*

Fifteen patients (8 male, 7 female) had at least one T/iCa ≥2.4 with a total of 23/471 (4.9%) of the samples showing a T/iCa ≥2.4. The patients with a T/iCa ≥ 2.4 had a lower body weight, higher APACHE score, a higher citrate dose and citrate target, and a higher albumin; phosphate, lactate and pH and age were not significantly different between groups (see Table 3). Of the 23 samples with a T/iCa ≥ 2.4, 14 were ≥ 2.5 (61%), which is 3.0% of the total of 471 samples.

## 4. Discussion

The present retrospective analysis shows that other variables than the citrate may contribute to the total versus ionized Ca ratio (T/iCa), a marker used to monitor systemic citrate accumulation during regional citrate anticoagulation of the CRRT circuit. Alterations in albumin, phosphate, pH, lactate and severity of disease all appeared to explain changes in the T/iCa as well. Their interrelation is complex, reflecting that calcium in blood exists in 3 distinct fractions (as ionized calcium, bound to albumin and bound to various anions such as phosphate, lactate and citrate) and that pH can influence these interactions [9]. Thus, these variables may influence the T/iCa directly (pH, albumin, phosphate), may modulate the citrate concentration in the blood directly (citrate administration and APACHE II as marker of metabolism) or change both in parallel (lactate, both biochemically and as a parameter of metabolism). In the light of these findings, besides a higher citrate dose, high pH and high phosphate, albumin and APACHE may contribute to a rising T/iCa ratio. In case of a high ratio alterations in these variables should also be considered.

Ideally, from a biochemical perspective, we should have measured systemic citrate concentrations as one of the determinants of the T/iCa. However, citrate concentrations are not available in clinical practice. We therefore used the calculated delivered citrate dose as proxy, (in mmol/L and corrected this dose for body weight), and in a second model the citrate target (the targeted citrate concentration in mmol/L in the circuit blood), which is continuously available in clinical practice. The systemic citrate concentration depends on the amount of citrate delivered minus the amount removed by filtration, and subsequent citrate metabolism. Despite the limitation that citrate concentration is not available, using citrate dose and citrate target in our models has the advantage that both are available in clinical practice and modifiable.

A higher citrate dose is expected to increase the risk of citrate accumulation. Our linear mixed model shows that an increase in citrate target of 2 mmol/L (for example from 2.5 to 4.5) increased the T/iCa by 0.1 (Fig. 3 left panel). This is confirmed by our findings showing a significantly higher citrate dose and target in the patients with a presumed risk of citrate accumulation, as defined by a T/iCa ratio ≥2.4 (lower panel Table 3) According to our standard protocol, citrate targets are generally only increased by steps of 0.5 mmol/L. Thus, when patients with a presumed decreased metabolic capacity for citrate (suspected liver failure) are excluded, the contribution of the citrate target to the T/iCa ratio, though statistically significant, is small in the range of clinical citrate targets.

Our results also show that patients in the higher T/iCa group have a significantly lower body weight, possibly a reflection of relatively higher citrate load in a smaller body compartment. This suggests that the standard procedure in our center to adjust blood flow to body weight, may be insufficient.

Our model also demonstrates that the relation between T/iCa and citrate dose depends on the phosphate concentration (Fig. 2A). We found that in the presence of higher phosphate concentrations, an anion that also binds citrate, a higher citrate dose will lead to a higher the rise in T/iCa ratio. On the other hand, a decline in phosphate concentration after initiation of CVVH, may mask a possible accumulation of citrate.

Our study also shows that the T/iCa is related to surrogate markers of metabolism, the APACHE II score and lactate concentration. As expected, T/iCa was higher when APACHE and lactate were high. Previous studies found liver failure to be a risk factor for citrate accumulation [17]. However, according to the local protocol, patients with liver failure were excluded from CVVH with citrate anticoagulation but patients with shock were not. Other studies have shown that patients with higher lactate levels are more likely to develop citrate accumulation in the setting of citrate CVVH [18,19]. Besides being a marker of liver function, lactate is also a marker for anaerobic metabolism. Citrate is metabolized in the Krebs cycle and possibly by gluconeogenesis [20], and its metabolism is oxygen dependent. Its metabolism is therefore compromised under anaerobic conditions.

In our study, most of the measured lactate levels were within the normal range and interpretation should be made with caution, though it is clear from our data that, in case of acidosis, a rising lactate was associated with a higher increase in T/iCa.

In addition, pH, albumin and phosphate may affect the T/iCa ratio directly, independent of citrate. Acidemia decreases protein binding of calcium, thereby increasing iCa relative to total Ca and decreasing the T/iCa [12,13]. This biochemical effect is opposite to the metabolic consequence of citrate accumulation, which is associated with acidemia and an increased T/iCa. Our findings from the second LMM indeed demonstrated that higher pH was associated with a higher T/iCa ratio; more precisely an increase in pH of 0.2 was associated with an increase T/iCa by 0.12. This clinically relevant change would induce a higher change in the T/iCa ratio than that caused by a 2 mmol/L increase in citrate target concentration. This finding is important because pH can fluctuate markedly in the ICU population due to alterations in ventilator settings [12,13]. In addition, improved metabolic control after the start of citrate CVVH will cause a rise in pH and consequently a rise in T/iCa without necessarily inferring citrate accumulation.

Another finding of our study is that, low albumin levels were associated with lower T/iCa. Approximately 40% of calcium in extracellular fluid is protein-bound, mainly to albumin, and a lowering of serum albumin causes a lowering of total Calcium, but has a lesser effect on iCa [7]. Albumin can fluctuate markedly in the ICU population and the use of albumin as a resuscitation fluid in the setting of severe sepsis and septic shock [21,22] can thereby increase the T/iCa ratio. Recognition of this association is therefore clinically relevant and should not be solely interpreted as citrate accumulation. We found that this relation is even more complex because it is modulated by phosphate and APACHE (Fig. 2B). The association of the albumin and the T/iCa is more pronounced if phosphate is low. This finding is clinically relevant

because phosphate may decrease, especially when high concentrations due to AKI drop after the start of CVVH [[23], [24], [25]], but also as a consequence of altered ventilator settings, hyperventilation causing hypophosphatemia [26,27]. Assuming that phosphate stays within the mid-range (33% to 66% quantile), a 10 g/L rise in albumin, is associated with an increase in the T/iCa by 0.1, a modest effect. This increase is more extreme when phosphate values are low.

This study has several limitations. Most importantly, when comparing the high and low T/iCa groups, the number of patients and samples in the high T/iCa group are low. However, the LMM model looks at the T/iCa as a continuous variable and thereby includes all samples. Risk of accumulation, defined as a T/I Ca ≥2.4, was seen in 15% of the patients and less than 5% of samples. In comparison to other studies this percentage seems high [28] likely because some patients received higher dosing of citrate as part of a randomized controlled study. Furthermore, the cut-off of 2.4 in our center is lower than the generally used cut-off of 2.5. In our population 14 samples were ≥2.5 which is 3.0% of the total. In addition, the delivered amount of citrate is higher in hemofiltration because hemofiltration requires higher blood flows than dialysis and therefore a higher citrate dose for a similar clearance [3]. Removal in our setting comprised about 38% of the delivered dose.

CVVH is possibly also associated with more clogging which may hamper citrate clearance. However comparable clearances for small and middle size solutes were found, when comparing CVVH to continuous venovenous hemodialysis [29]. In CVVH, clogging is detected by increasing transmembrane pressures, which were routinely monitored. A further limitation is that, in most patients, data point acquisition took place during different CVVH runs, possibly exacerbating the influence of unmeasured effects. In addition, as a single center study, findings can be influenced by local clinical practice such as the use of phosphate-free substitution fluids, nurse led adjustments to ventilation and the use of albumin for resuscitation. Moreover, the study design was retrospective and the large majority of values used in this database are from blood drawn at 6 am. Consequently, the values used in the database were acquired at different periods after initiation of citrate CVVH, which may be a strength as well. Furthermore, down time was not taken into account when calculating citrate dose. Next, patients with longer duration of citrate CVVH, represent more data points in the database, a possible source of bias. For the LMMs, data rows with at least one missing value in the parameters involved were deleted from the analysis, assuming that the reason for their absence was not related to either the unobserved value or to the other variables. The validity of the findings based on this assumption is shown by the similarity between findings in the full sample and LMM sets (comparing T/iCa below 2.4 and ≥2.4).

Finally, this retrospective study can only demonstrate associations between the measured parameters, not causality. Conclusions based on these findings as to cause and effect should be drawn with caution. Nevertheless, the different relations have plausible explanations.

## 5. Conclusions

The present retrospective analysis shows that, besides citrate, alterations in albumin, phosphate, pH, and severity of disease and to a lesser extent lactate are associated with changes in T/iCa. Its increase therefore does not necessarily reflect citrate accumulation nor does a normal ratio exclude accumulation. While the association between high APACHE with a higher T/iCa ratio likely reflects accumulation due to impaired citrate metabolism, rises in albumin, pH and phosphate are associated with increases in T/iCa ratio that do not necessarily reflect accumulation, but have a biochemical explanation. The association with pH is complex and can be difficult to interpret for the clinician, because, on the one hand, accumulation of citrate may be due to impaired metabolism causing metabolic acidosis and citrate accumulation may lead to acidosis because it is a strong anion, while, on the other hand and counterintuitively, higher pH is on biochemical grounds associated with an increasing T/iCa ratio. Clinical suspicion for citrate accumulation in citrate CVVH remains paramount but the interpretation of the T/iCa ratio should take these complex interactions into account. Most importantly, citrate is not toxic in itself. Toxicity is related to associated hypocalcemia and metabolic acidosis. Thus, if calcium can be supplemented and acid base is under control, an increased T/iCa ratio can be accepted under close monitoring of vital signs.

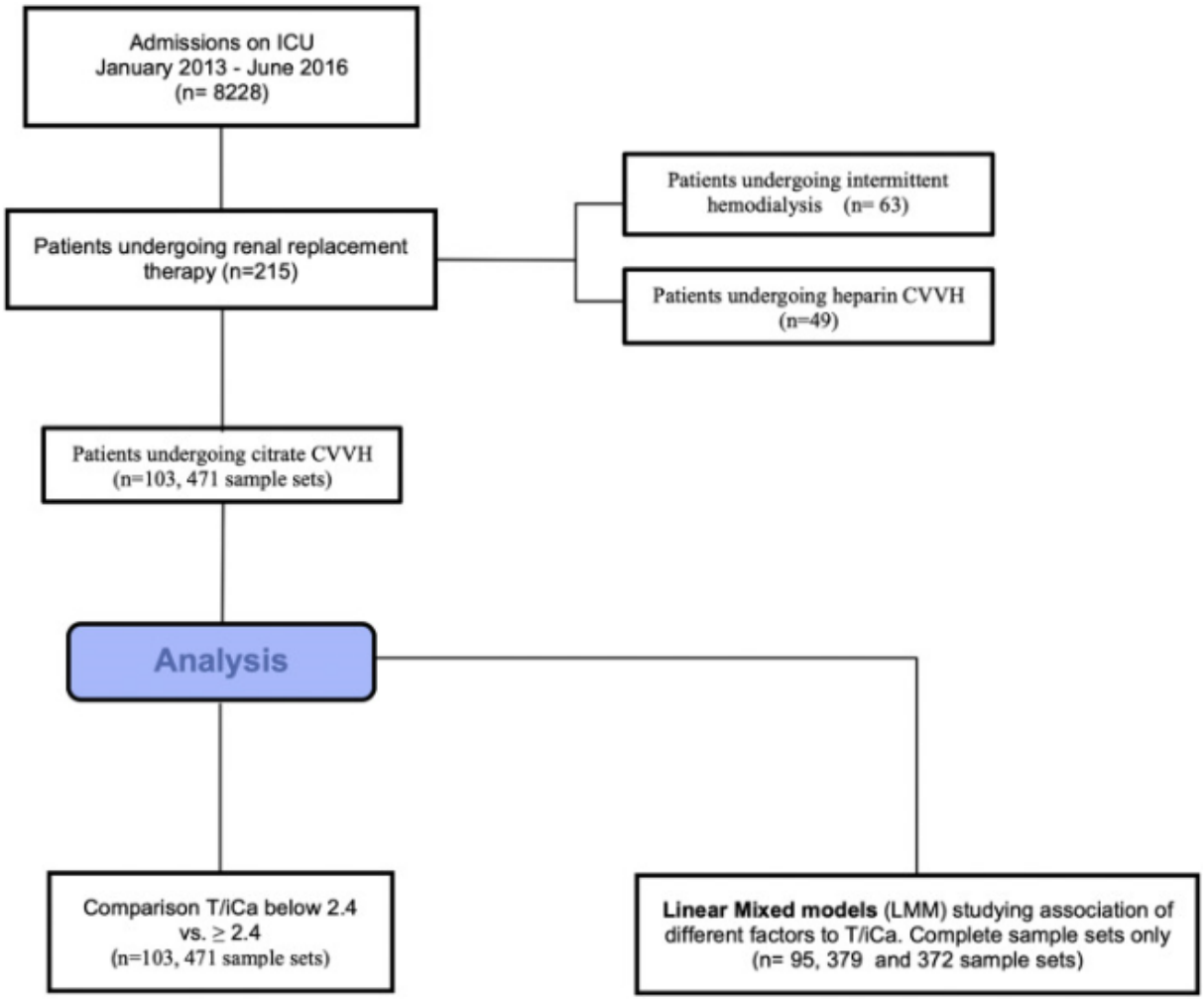


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Fig. 1. Study inclusion.

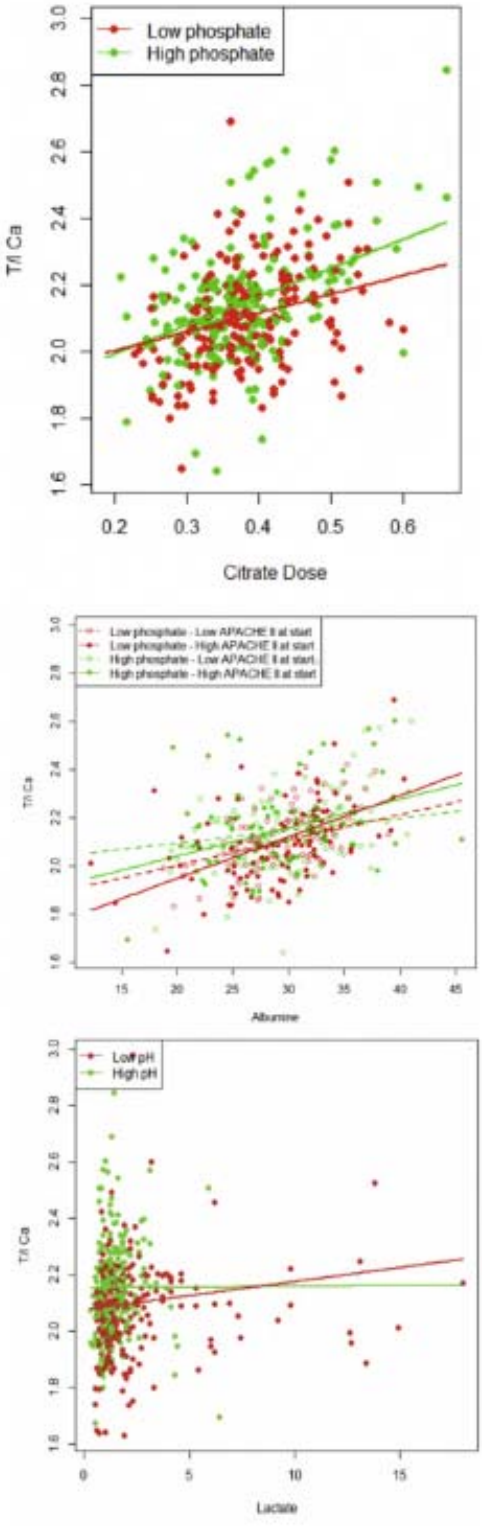


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Fig. 2. 2D graphs depicting interactions in LMM with citrate dose (mmol/kg/h). and phosphate on T/iCa ratio (A), combined effects of albumin, APACHE II at start and phosphate on T/iCa ratio (B), combined effects of lactate and pH on T/iCa ratio (C) – all other variables are kept at their average value.

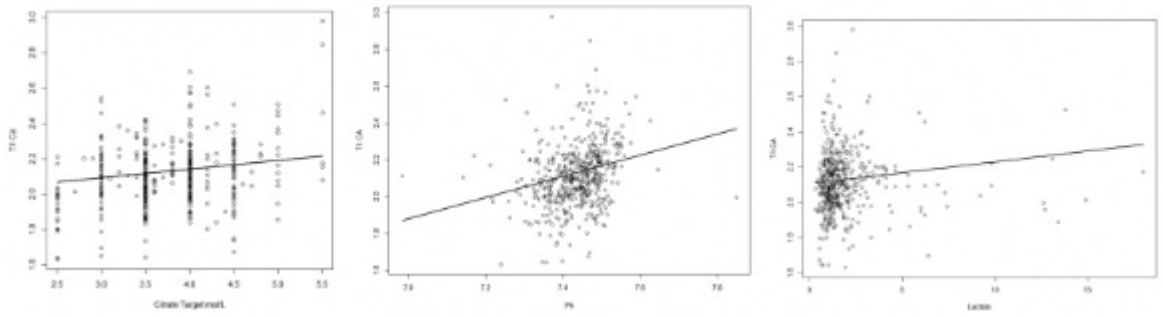

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Fig. 3. Scatter plots of T/iCa versus citrate target, pH and lactate. The lines describe the estimated associations, setting the other parameters at the average levels observed in the data set.

Table 1. Baseline characteristics.

| | |
|---|---|
| **Total no. Patients** | 103 |
| **Age** | 69 (63–76) |
| **Gender** | M 65 (63%) F 38 (37%) |
| **KDIGO stage AKI** $_{\text{on initiation of CVVH}}$ | II: 30 (29%) III: 73 (71%) |
| **APACHE II** $_{\text{admission}}$ | 22 (18–30) |
| **APACHE II** $_{\text{initiation CVVH}}$ | 26 (22–32) |
| **vasopressor/inotropic** $_{\text{at initiation of CVVH}}$ | 91/103 (88%) |
| **admission diagnosis** | |
| **Cardiac** | 45/103 (43.7%) |
| **AMI** | 1/103 (0.9%) |
| **CABG (simple)** | 15/103 (14.6%) |
| **Complex cardiac surgery (valve, CABG+valve, endocarditis, other)** | 29/103(28.2%) |
| **Abdominal (including post-surgery, pancreatitis)** | 13/103 (12.6%) |
| **Respiratory** | 10/103 (9.7%) |
| **Neurological/neurosurgical** | 6/103 (5.8%) |
| **Renal** | 3/103 (2.9%) |
| **Major vascular** | 8/103 (7.8%) |
| **Sepsis and Septic Shock** | 14/103 (13.6%) |
| **Gynaecological** | 2/103 (1.9%) |
| **Trauma** | 2/103 (1.9%) |

Results in mean (SD), median (IQR) or number (%).

AMI: acute myocardial infarction.

CABG: coronary artery bypass graft.

Table 2. Study variables in the 471 sample sets.

| Variables | Mean (SD) or Median (25th –75th percentile) | Lowest | Highest | % < normal | % normal | % > normal |
|---|---|---|---|---|---|---|
| T/iCa | 2.10 (2.01–2.20) | 1.6 | 3.0 | – | – | – |
| citrate target (mmol/L) | 3.8 (3.5–4.0) | 2.5 | 5.5 | – | – | – |
| Citrate dose (mmol/kg/h) | 0.37 (0.33–0.42) | 0.19 | 0.66 | – | – | – |
| Albumin (g/L) | 29.2 (5.04) | 12.2 | 45.5 | 89 | 11 | 0 |
| Phosphate (mmol/L) | 0.88 (0.69–1.14) | 0.24 | 2.98 | 47 | 42 | 11 |
| pH | 7.44 (7.39–7.48) | 6.98 | 7.85 | 11 | 44 | 45 |
| Lactate (mmol/L) | 1.3 (1.00–1.98) | 0.3 | 18.0 | – | 75 | 25 |

Values in mean (SD), median (IQR).

Normal values: lactate 0.40–2.00 mmol/L; pH = 7.35–7.45; Albumin 35.0–52.0 g/L; Phosphate 0.87 –1.45 mmol/L.

Table 3. Comparison of patients developing a T/iCa < 2.4 and ≧2.4 in the full sample set.

| Total/ionizd Ca ratio (T/i Ca) | <2.4 | ≧2.4 | p-value |
|---|---|---|---|
| no. patients (M/F) | 88(57/31) | 15(8/7) | 0.40 |
| age | 69 (63–75) | 73 (59–82) | 0.40 |
| weight (kg) at ICU admission | 82.3 (16.4) | 72.3 (16.1) | **0.032** |
| APACHE II $_{CVVH}$ | 25 (21–31) | 32 (22–41) | **0.036** |
| | | | |
| no. data points | 448 | 23 | – |
| citrate target (mmol/L) | 3.70 (3.50–4.00) | 4.00 (3.50–4.50) | **<0.001** |
| citrate dose (mmol/kg/h) | 0.37 (0.32–0.42) | 0.46 (0.39-0.56) | **<0.000001** |
| albumin (g/L) | 28.96 (4.91) | 33.23 (5.93) | **0.006** |
| phosphate (mmol/L) | 0.88 (0.69–1.14) | 0.95 (0.78–1.53) | 0.06 |
| pH | 7.44 (7.39–7.48) | 7.47 (7.44–7.51) | 0.09 |
| lactate (mmol/L) | 1.3 (1.0–1.9) | 1.3 (1.0–2.5) | 0.82 |

values in mean (SD), median (IQR), $p < 0.05$ in bold.

## Ethics approval and consent to participate

The study protocol was approved by the local institutional review board (Commissie Medische Ethiek Ziekenhuis Oost-Limburg, approval no. 16/053 U). The need for informed consent was waived because the study analyzed variables collected during standard medical care.

## Availability of data and material

The datasets used and/or analyzed for study are available from the corresponding author on reasonable request.


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## Declaration of Competing Interest

H.O. received Speaker's honorary fee and participated in advisory meetings for Fresenius, Baxter/ Gambro and Dirinco.


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