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TRANSFUSION

ORIGINAL RESEARCH

TRANSFUSION COMPLICATIONS

Ratios of calcium to citrate administration in blood transfusion for traumatic hemorrhage: A retrospective cohort study

Husam Alghanem[1] | **Nathan Chi-Ping Liu**[2] | **Atul Gupta**[2] | **Chuanhong Liao**[3] | **Geoffrey David Wool**[4] | **Daniel Steven Rubin**[2] | **Timothy Carll**[4]

[1]Department of Anesthesiology, Pain Medicine, and Perioperative Medicine, Henry Ford Health System, Detroit, Michigan, USA

[2]Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois, USA

[3]Department of Public Health Sciences, University of Chicago, Chicago, Illinois, USA

[4]Department of Pathology, University of Chicago, Chicago, Illinois, USA

Correspondence
Husam Alghanem, Department of Anesthesiology, Pain Medicine, and Perioperative Medicine, Henry Ford Health System, Detroit, MI, USA.
Email: alhusam@umich.edu

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Abstract

Background: Massive transfusion with citrated blood products causes hypocalcemia, which is associated with mortality. Recognition of this problem has led to increased calcium administration; however, the optimal dosing is still unknown.

Study Design and Methods: This retrospective, single-center study included level 1 trauma patients in 2019 and 2020 who underwent an operation within 12 h of arrival and received a transfusion. Preoperative and intraoperative administrations were totaled to calculate the ratio of administered calcium to the number of blood transfusions for each patient. The citrate content of each blood component was estimated to calculate a second ratio, the ratio of administered calcium to administered citrate. Receiver Operating Characteristic (ROC) curves were performed on both ratios to determine the optimal cutoff values for predicting severe hypocalcemia (ionized calcium <0.9 mmol/L) and hypercalcemia (>1.35 mmol/L) at the end of the intraoperative period.

Results: A total of 506 trauma activations were included, receiving a mean of 17.4 citrated blood products and 16.3 mmol of calcium (equivalent to 2400 mg of calcium chloride). No ratio was statistically significant in differentiating severely hypocalcemic patients from the rest. A calcium to blood ratio of

Abbreviations: AUC, area under ROC curve; ER, emergency room; FFP, fresh frozen plasma; IR, interventional radiology; OR, operating room; PF24, plasma frozen within 24 hours; PLT, plateletpheresis unit; pRBC, packed red blood cell; ROC, Receiver Operating Characteristic.

0.903 mmol of administered calcium per citrated blood product differentiated hypercalcemic patients from the rest.

Discussion: Quantifying received calcium and citrated blood products was insufficient to predict severe hypocalcemia, suggesting other contributions to hypocalcemia. We demonstrated an upper-limit ratio for calcium administration in traumatic hemorrhage; however, further studies are required to determine what calcium dosing regimen results in the best outcomes.

KEYWORDS

1:1:1 ratio, citrate toxicity, hypercalcemia, hypocalcemia, hypomagnesemia, massive transfusion, packed red blood cells, plasma

1 | INTRODUCTION

From 2001 to 2020, traumatic injury was the leading cause of death in the United States between the ages of 1 and 44 years.[1] The majority of transfused blood products worldwide utilize citrate anticoagulant to chelate calcium, thereby blocking plasmatic coagulation and thrombin generation in stored blood products. The harms of citrate-induced transfusion-related hypocalcemia have been increasingly recognized.[2–5]

Citrate toxicity is more likely to occur with a high rate (mL/min) of transfusion, which overwhelms the liver's capacity to metabolize the citrate.[6,7] While citrate administration in the absence of hemorrhage may not decrease total serum calcium concentration, it does decrease the ionized calcium concentration, the relevant physiologic parameter.[6,8] Citrate administration with concurrent hemorrhage will additionally result in the loss of citrate-calcium complexes, lowering both total serum calcium and ionized calcium concentrations.

Clinical complications of hypocalcemia include arrhythmias, decreased ventricular contractility, decreased vascular tone, and coagulopathy, all of which can lead to hypotension and shock.[2,9,10] Severe hypocalcemia, specifically an ionized calcium <0.9 mmol/L, during or after blood transfusion for trauma is an independent predictor of mortality.[11] Iatrogenic hypercalcemia due to calcium oversupplementation is rare;[12] however, it has been associated with mortality[4] and increased attention to hypocalcemia may lead to increased occurrence. Despite significant research on calcium derangements in massive transfusion, there is no consensus on how much calcium should be supplemented.

Administration of citrated blood products can also cause clinically significant hypomagnesemia by chelating magnesium, leading to ventricular arrhythmias, coagulopathy, and refractory hypocalcemia.[9,13–20] Total serum magnesium is an imperfect measurement of a patient's magnesium status given that the primary effects are determined by intracellular ionized magnesium, which is difficult to measure.[20] Transfusion-related hypomagnesemia is frequently overlooked and most of the literature on citrate toxicity and massive transfusion does not mention magnesium.[2–4,21–28]

In component transfusion therapy, citrate is primarily found in plasma-rich products, which includes thawed fresh frozen plasma (FFP), thawed plasma frozen within 24 h (PF24), and thawed plasma.[11,12,27–33] However, calcium replacement regimens and citrate load calculations are often based on the number of packed red blood cell (pRBC) transfusions, ignoring the number of plasma transfusions or incorrectly equating pRBC and plasma citrate quantities.[2,3,5,21–23] While the citrate content of pRBC units depends on the collection method, the specific anticoagulant preservative used, and the specific additive solution used, our calculations demonstrate that at our institution a unit of FFP or PF24 has approximately three to four times as much citrate as a unit of pRBC (Appendix S1), similar to what has been previously reported in the literature.[30,31]

We sought to determine the ratio of calcium to blood administration that was least likely to result in hypercalcemia or severe hypocalcemia in a retrospective study of patients undergoing transfusion for traumatic hemorrhage. This population was chosen because of the high prevalence and volumes of blood transfusions, as well as the low rate of preexisting metabolic conditions that may influence the body's regulation of calcium and citrate. We hypothesized that patients who had greater numbers of transfusions would have more severe hypocalcemia and hypomagnesemia and a stronger correlation between the ratio of calcium to blood administration and the resulting serum ionized calcium.

2 | STUDY DESIGN AND METHODS

This study was approved by the University of Chicago Institutional Review Board, which waived informed

consent as this study used only retrospective data that was originally obtained for patient care. This retrospective single-center cohort study adheres to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) specifications.[34]

Patients were identified by either of two custom electronic medical record reports. The first identified all emergency room (ER) arrivals who had a standardized trauma documentation form initiated. The second identified all emergency surgeries with the trauma surgery service, so as to capture patients who bypassed the ER and arrived directly to the operating room (OR). Of note, all patient electronic medical records had already been merged with their true identities prior to the initiation of this study, because many trauma patients are initially assigned placeholder identities. Included patients were those who arrived as a level 1 trauma activation to the University of Chicago Medical Center between January 1, 2019 and December 31, 2020, were ≥16 years of age, went to the OR or interventional radiology (IR) or both, and who received at least one blood product prior to or during their intraoperative period. Patients who were initially level 2 trauma activations but received at least three blood products were treated as level 1 trauma activations and included. The following conditions caused patients to be excluded: death in the ER, first visit to the OR or IR > 12 h after ER arrival, current pregnancy, readmission for a prior injury, or no calcium measurements both intraoperatively and within 12 h postoperatively.

If a patient left an OR or IR for less than 30 min and had no calcium measurements before going back to an OR or IR, then both intraoperative periods were merged in the analyses as one intraoperative period. All blood products and calcium administrations were totaled for the intraoperative and the preoperative periods, including those documented by transferring hospitals and emergency services. Nursing and physician notes (preoperative, intraoperative, and postoperative), medication administration records, and scanned blood transfusion documents were assessed to confirm blood product transfusions and medication administrations when possible.

Commercial formulations of calcium gluconate contain a mixture of calcium gluconate and calcium saccharate tetrahydrate such that 1g contains a total of 2.32 mmol of calcium. Since 1 g of calcium chloride dihydrate contains 6.8 mmol of calcium, calcium gluconate administrations in grams were converted to calcium chloride equivalents in grams by dividing by 3.[28] The calcium to blood administration ratio was calculated as millimoles of administered calcium divided by the total number of citrated blood products administered. To better separate those patients who did not receive any calcium at all but had disparate levels of transfusion, these patients had their calcium to blood ratio calculated as if they had received 0.68 mmol of calcium (equivalent to 100 mg of calcium chloride dihydrate).

Transfused pRBC came from multiple sources but were primarily collected in CPD solution with AS-1 additive solution. The majority of platelet products were single-donor apheresis platelets in platelet additive solution C. For some secondary analyses, blood product transfusion counts were converted into estimated citrate content. Appendix S1 details the calculations showing mean citrate contents of 1.32 mmol for pRBC, 5.15 mmol for FFP/PF24, 4.14 mmol for a plateletpheresis unit (PLT), 1.49 mmol for a cryoprecipitate pool, and 7.35 mmol for whole blood. These citrate contents were simplified to FFP/PF24 equivalents: 0.3 for pRBC, 1 for FFP/PF24, 0.8 for PLT, 0.3 for cryoprecipitate pool, and 1.4 for whole blood. A calcium to citrate administration ratio was calculated as millimoles of administered calcium divided by total FFP/PF24 equivalents of citrate.

Our institution became a level 1 trauma center on May 1, 2018, seven months prior to the study period. Two institutional blood bank policies and procedures changed during the period of the study. On July 24, 2020, the standard Massive Transfusion Protocol pack composition changed from 6 pRBC, 4 FFP/PF24, and 1 PLT to 6 pRBC, 6 FFP/PF24, and 1 PLT. On September 1, 2020, low-titer Group O whole blood units became available in the ER, exclusively for trauma patients with use at the discretion of the trauma surgeon. Our institution did not have guidance or a protocol regarding calcium supplementation.

2.1 | Outcomes

The primary outcome of severe hypocalcemia, hypercalcemia, and intermediate calcium level was determined preferentially using the first postoperative ionized calcium measurement. If that was not available, then the last intraoperative ionized calcium was used, then the first postoperative total serum calcium, and then the last intraoperative total serum calcium. Intraoperative and preoperative total calcium, ionized calcium, total magnesium, hemoglobin, and arterial pH were captured. Postoperative labs were only included if they were drawn within 12 h of the end of the intraoperative period. In the case of multiple sets of postoperative labs, only the very first measurements were captured. Central lab blood gas testing was performed with a GEM 5000 (Werfen/Instrumentation Laboratory, Munich, Germany). Point-of-care ionized calcium levels were checked on epoc® Blood Gas Analyzers (Siemens, Erlangen, Germany), with a reference range of 1.15–1.35 mmol/L. For our analyses, an ionized calcium <0.9 mmol/L was labeled as severe

hypocalcemia as this threshold has been correlated with mortality[11] and >1.35 mmol/L was labeled as hypercalcemia, as hypercalcemia above the local reference range has been correlated with mortality.[4] The third outcome category, an ionized calcium of 0.9–1.35 mmol/L, is a broader range than normocalcemia, so it was labeled as the intermediate calcium outcome. Total serum calcium and total serum magnesium were measured with a cobas® 8000, C702 module (Roche Diagnostics Corporation, Basel, Switzerland). The total serum calcium local reference range of 8.4–10.2 mg/dL (2.1–2.6 mmol/L) was used to determine the primary outcome when no ionized calcium values were available. The local reference range of total serum magnesium was 1.6–2.5 mg/dL (0.66–1.0 mmol/L).

Mortality was measured at three time points: intraoperatively, within 72 h of admission, and within the admission. Other captured outcomes were measured from the initial patient contact until 24 h postoperatively, including atrial fibrillation/flutter, other serious arrhythmias (excluding premature atrial and ventricular contractions), defibrillations, cardioversions, and chest compressions.

2.2 | Statistical analysis

Population characteristics were reported as percentages (%) for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables. Receiver Operating Characteristic (ROC) curves were performed on calcium to blood and calcium to citrate administration ratios to determine the optimal cutoff values for differentiating severely hypocalcemic patients from the rest, and then performed again to differentiate hypercalcemic patients from the rest. The area under the ROC curve (AUC), the optimal thresholds using the Liu method for empirical cutpoint estimation, and the sensitivity and specificity of said thresholds were reported for each ROC curve. Patients were divided into two subgroups based on the median total number of transfused blood products and ROC curve analyses were repeated for each subgroup.

Because of the high likelihood of nonparametric data containing outliers, quantile linear regression using quantiles of 0.25, 0.5, and 0.75 was performed on the magnesium outcome, using the variables most likely to predict the electrolyte level: presenting magnesium level and the total administration of albumin, blood products, and FFP/PF24 citrate equivalents. Any patients who received magnesium supplementation were excluded from the magnesium outcome regression. The analysis was repeated for the high transfusion volume subgroup.

3 | RESULTS

During the study period, 6032 patients aged 16 years and above had trauma activations and 506 patient admissions (505 unique patients) met all study criteria (Figure 1). The primary outcome was determined by the first postoperative ionized calcium in 23 patients, then the last intraoperative ionized calcium in 445 patients, then the first postoperative total serum calcium in 38 patients, and then the last intraoperative total serum calcium in zero patients. The primary outcome was severe hypocalcemia in 58 patients, hypercalcemia in 71 patients, and intermediate calcium level in 377 patients. Of the intermediate patients, 157 had mild hypocalcemia (ionized calcium 0.9–1.14 mmol/L) and 220 had normal calcium levels within the local reference range. Six patients were excluded from magnesium regression analyses because they received magnesium supplementation during the ER or intraoperative periods and 80 were excluded because they did not have magnesium levels checked intraoperatively or within 12 h postoperatively. Patient characteristics are shown in Table 1. Table 2 shows how blood component transfusion ratios, calcium outcome, and mortality varied in patients with different total numbers of blood transfusions. For subgroup analyses, patients were divided based on the median total number of transfusions, with 257 patients receiving 1–9 total transfusions and 249 patients receiving 10 or greater transfusions.

3.1 | Calcium to blood and calcium to citrate administration ratio thresholds

The ROC curves of calcium to blood ratios for predicting severe hypocalcemia did not reach statistical significance when analyzed for all patients ($p = 0.178$, Figure 2A) or for either subgroup. The ROC curve of calcium to citrate ratios for predicting severe hypocalcemia did not reach statistical significance for all patients ($p = 0.225$, Figure 2B) or for either subgroup. Table 3 lists the ROC curve results for predicting severe hypocalcemia.

The ROC curves of calcium to blood ratios for predicting hypercalcemia demonstrated statistically significant thresholds of 0.903 mmol of administered calcium per blood product for all patients (Figure 2C), 1.46 for lower volume transfusion patients (1–9 units), and 0.955 for higher volume transfusion patients (10 or more units). ROC analyses using calcium to citrate ratios for predicting hypercalcemia were not statistically significant for all patients (Figure 2D) or the lower volume transfusion patients, but revealed a statistically significant threshold of 1.44 mmol of calcium per FFP/PF24 equivalent of

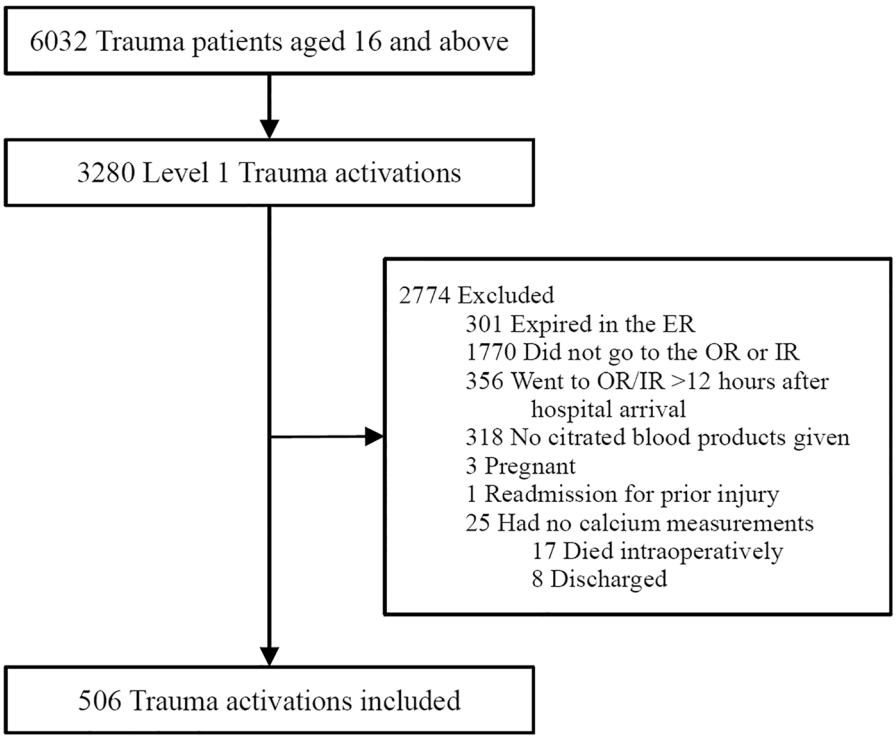

FIGURE 1 Consort flow diagram of patients screened for inclusion in the study. ER, emergency room; OR, operating room; IR, interventional radiology.

citrate in the higher volume transfusion patients. Table 4 lists the ROC curve results for predicting hypercalcemia.

3.2 | Quantile regression of magnesium levels

Quantile linear regression analyses utilizing quantiles of 0.25, 0.5 (median), and 0.75 demonstrated that albumin administration was most strongly associated with a lower 0.25 quantile magnesium level (Table 5), but that none of the assessed variables were associated with a change in the 0.5 (median) or 0.75 quantiles. The 0.25 quantile was inversely associated with the total number of blood products, but not with the total number of FFP/PF24 citrate equivalents. In the subgroup analysis of higher volume transfusion patients, however, the 0.25 quantile was inversely associated with the total number of FFP/PF24 citrate equivalents and not with the total number of blood products.

4 | DISCUSSION

Our exploratory study found calcium administration ratio thresholds that correlated with avoidance of hypercalcemia but was unable to determine statistically significant thresholds for avoiding severe hypocalcemia. Hypercalcemia in trauma is primarily thought to be an iatrogenic complication,[12] so it is to be expected that accurate documentation of calcium administration would strongly correlate and explain a patient's final calcium outcome. One strength of our study is that we performed manual, not automated, individual chart abstraction, because electronic medical record documentation during a hectic massive transfusion is sometimes nonstandard. One source of error is that point of care arterial blood tests immediately after venous administration of calcium may result in artificially high calcium values prior to the redistribution of calcium throughout the body. Severely injured patients would likely have more frequent administrations of intravenous calcium and more frequent blood tests. This would cause an underestimation of the optimal calcium to blood administration ratio, so further work may benefit from excluding calcium values that are outliers within a patient's time course.

Hypocalcemia in trauma is a more complicated phenomenon with multiple etiologies besides citrate toxicity. Prior studies have shown that some trauma patients are hypocalcemic prior to the first administration of blood products,[35,36] which may be explained by calcium shifting intracellularly in ischemic tissues or rhabdomyolysis.[2] It is unclear if calcium administration in a patient with ongoing tissue cell death might worsen reperfusion injury. Administration of colloids and most crystalloids causes hypocalcemia via dilution.

Hypomagnesemia, a known complication of citrate toxicity, can cause refractory hypocalcemia via

TABLE 1 Population characteristics stratified by primary outcome.

Demographics	All patients ($N = 506$)	Severe Hypocalcemia[a] ($N = 58$)	Intermediate[b] ($N = 377$)	Hypercalcemia[c] ($N = 71$)
Age, years	32.8 ± 14.3	33.6 ± 12.8	32.9 ± 14.7	31.3 ± 13.6
Male sex	426 (84.2%)	50 (86.2%)	318 (84.4%)	58 (81.7%)
Penetrating trauma mechanism	397 (78.5%)	40 (69.0%)	300 (79.6%)	57 (80.3%)
Presenting Glasgow Coma Scale total score	15 [11, 15]	14 [3, 15]	15 [13, 15]	14 [3, 15]
Preoperative hours	1.4 ± 2.0	2.3 ± 3.0	1.3 ± 1.8	0.9 ± 1.6
Intraoperative hours	3.8 ± 1.9	3.1 ± 2.1	3.9 ± 1.8	3.7 ± 1.9
Intraoperative location				
Operating room	465 (91.9%)	50 (86.2%)	350 (92.8%)	65 (91.5%)
Interventional radiology	21 (4.2%)	7 (12.1%)	14 (3.7%)	0 (0.0%)
Both	20 (4.0%)	1 (1.7%)	13 (3.4%)	6 (8.5%)
Extent of surgery or procedure				
Intracranial	28 (5.5%)	7 (12.1%)	19 (5.0%)	2 (2.8%)
Intrathoracic	145 (28.7%)	21 (36.2%)	94 (24.9%)	30 (42.3%)
Intraabdominal	323 (63.8%)	37 (63.8%)	236 (62.6%)	50 (70.4%)
Total blood products administered				
Whole blood[d]	0.2 ± 0.8	0.3 ± 1.2	0.2 ± 0.7	0.2 ± 0.6
Packed red blood cells	9.0 ± 11.5	16.3 ± 17.2	6.9 ± 8.2	14.3 ± 16.2
FFP/PF24	7.1 ± 8.8	12.6 ± 13.6	5.5 ± 6.6	11.3 ± 11.1
Platelets	0.9 ± 1.5	1.7 ± 2.2	0.7 ± 1.2	1.5 ± 2.0
Cryoprecipitate	0.2 ± 0.5	0.3 ± 0.6	0.1 ± 0.5	0.3 ± 0.8
5% Albumin (250 mL)	1.2 ± 1.8	1.2 ± 2.0	1.2 ± 1.8	1.2 ± 1.8
Total calcium chloride administered (mmol)	14 ± 24	29 ± 39	8.8 ± 16	29 ± 35
Total calcium gluconate administered (mmol)	2.0 ± 3.2	2.0 ± 3.2	2.0 ± 3.4	1.8 ± 3.2
Patients receiving cardiac compressions				
Preoperative	40 (7.9%)	10 (17.2%)	16 (4.2%)	14 (19.7%)
Intraoperative	31 (6.1%)	13 (22.4%)	7 (1.9%)	11 (15.5%)
Postoperative	47 (9.3%)	17 (29.3%)	17 (4.5%)	13 (18.3%)
Patients undergoing cardioversion				
Preoperative	13 (2.6%)	1 (1.7%)	7 (1.9%)	5 (7.0%)
Intraoperative	13 (2.6%)	6 (10.3%)	0 (0.0%)	7 (9.9%)
Postoperative	13 (2.6%)	5 (8.6%)	6 (1.6%)	2 (2.8%)
Intraoperative mortality	24 (4.7%)	12 (20.7%)	4 (1.1%)	8 (11.3%)
Mortality during admission	62 (12.3%)	20 (34.5%)	28 (7.4%)	14 (19.7%)
Postoperative day of death (when applicable)	0 [0, 2.5]	0 [0, 0]	1.5 [0, 4]	0 [0, 3]
Postoperative day of discharge (when applicable)	12 [7, 21]	13 [7, 25]	12 [6, 20]	16 [10, 25]

Note: Variables are presented as *N* (%), mean ± SD, or median [25th, 75th percentile].
Abbreviation: FFP/PF24, fresh frozen plasma or plasma frozen within 24 h.
[a]Ionized calcium <0.9 mmol/L.
[b]Ionized calcium 0.9–1.35 mmol/L.
[c]Ionized calcium >1.35 mmol/L.
[d]Whole blood was only available for 17% of the study period.

TABLE 2 Patient outcomes stratified by the total number of transfusions.

Total number of transfusions	1–5	6–10	11–20	21–30	31–40	41–60	61+
Number of patients	173	99	99	48	31	29	27
Ratio of FFP/PF24 to pRBC							
Median	1.00	0.80	0.83	0.85	0.88	0.83	0.72
Interquartile range	0.33–1.00	0.60–1.00	0.70–1.00	0.75–1.00	0.71–0.94	0.73–0.93	0.66–0.97
Ratio of PLT to pRBC							
Median	0.00	0.00	0.13	0.10	0.13	0.13	0.12
Interquartile range	0.00–0.00	0.00–0.00	0.00–0.17	0.08–0.17	0.11–0.16	0.08–0.15	0.10–0.14
Calcium outcome							
Severe hypocalcemia[a]	10.4%	5.1%	8.1%	8.3%	16.1%	24.1%	40.7%
Intermediate[b]	86.7%	84.8%	69.7%	64.6%	64.5%	37.9%	44.4%
Hypercalcemia[c]	2.9%	10.1%	22.2%	27.1%	19.4%	37.9%	14.8%
Mortality at three time-points							
Intraoperative	0.6%	0.0%	1.0%	4.2%	19.4%	24.1%	25.9%
72 h from admission	2.9%	2.0%	4.0%	14.6%	22.6%	34.5%	51.9%
End of admission	3.5%	5.1%	4.0%	16.7%	32.3%	37.9%	66.7%

Abbreviations: FFP/PF24, fresh frozen plasma or plasma frozen within 24 h; PLT, apheresis platelet; pRBC, packed red blood cells.
[a]Ionized calcium <0.9 mmol/L.
[b]Ionized calcium 0.9–1.35 mmol/L.
[c]Ionized calcium >1.35 mmol/L.

multiple mechanisms, including inhibition of parathyroid hormone.[20] Despite this, magnesium replacement during massive transfusion is rarely considered or performed. Our study demonstrated that administrations of albumin, total blood products, and FFP/PF24 citrate equivalents are associated with a lower 0.25 quantile of magnesium levels in a traumatic hemorrhage population, confirming the findings of prior studies.[13]

A prior study of the ratio of calcium to citrate administration in traumatic hemorrhage did not find statistically significant correlations[28]; however, our patients received a greater number of blood transfusions and higher doses of calcium, which increased the likelihood that a patient's calcium status would be meaningfully affected by citrate toxicity and calcium administration. In our study, the calcium ratios resulting in hypercalcemia and severe hypocalcemia were further apart in the lower volume transfusion subgroup (1–9 blood transfusions) than in the higher volume transfusion subgroup (10 or more blood transfusions), reflecting that an absolute amount of excess calcium or citrate is needed for a patient to become hypercalcemic or severely hypocalcemic. The higher volume transfusion subgroup had stronger statistical associations between calcium to blood and calcium to citrate administration ratios and hypercalcemia, but weaker associations with severe hypocalcemia. Hypocalcemia in heavily transfused patients may be confounded by hypomagnesemia, ongoing blood loss removing citrate from the body, or a greater severity of traumatic tissue injury causing intracellular calcium shift.

Utilizing a calcium to citrate ratio did not yield an improvement in predicting hypocalcemia or hypercalcemia compared with the much simpler ratio of calcium to the total number of blood products. This may, in part, be due to the narrow range of FFP/PF24 to pRBC transfusion ratios observed at our institution, with 60% of patients receiving 0.7 to 1.0 plasma transfusions per pRBC. In addition, our detailed citrate content calculations in Appendix S1 have not been validated with direct testing. Despite consensus in the blood bank literature that plasma products contain more citrate than pRBC's, few studies have measured the ionized calcium and citrate content of different blood products.

While different blood components vary in their average citrate composition, individual blood products of the same component type vary in citrate composition based on the processing method and which additive solution is used. For example, a pRBC unit prepared with AS-3 (Nutricel, Haemonetics) has three times as much citrate as other pRBC units. This may explain a significant amount of variability in our dataset, as we did not determine the specific methods and solutions of the individual units of blood used in the study. Correcting for the average citrate content of each blood component type demonstrated a statistically significant ROC curve in a hypercalcemia subgroup analysis (Table 4) but did not increase the AUC.

This retrospective study did not determine any statistically significant thresholds for avoiding severe hypocalcemia. The determined threshold for avoiding

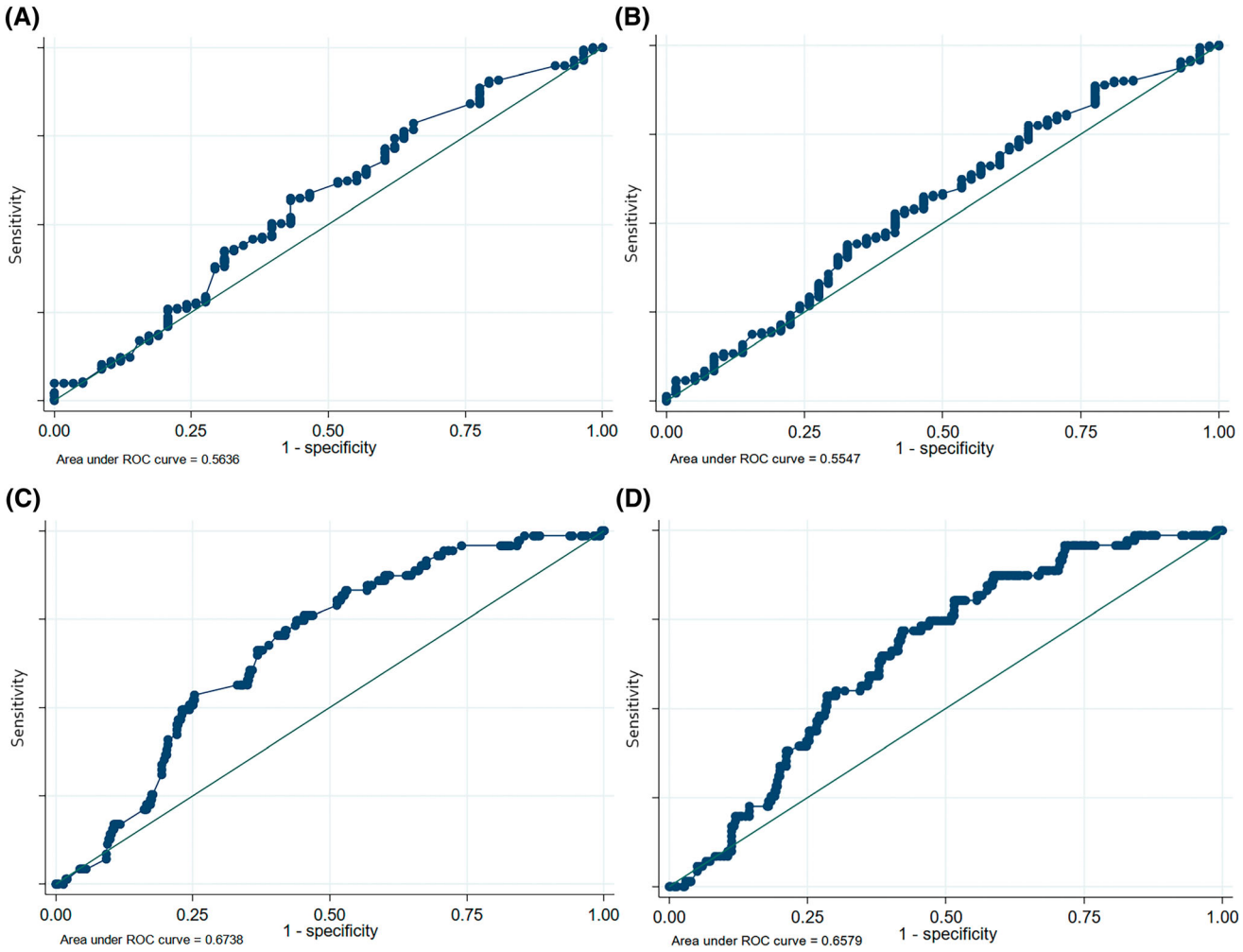

FIGURE 2 Receiver operating characteristic curves for calcium administration ratios. (A, top left) Calcium to blood ratio for avoidance of severe hypocalcemia. (B, top right) Calcium to citrate ratio for avoidance of severe hypocalcemia. (C, bottom left) Calcium to blood ratio for avoidance of hypercalcemia. (D, bottom right) Calcium to citrate ratio for avoidance of hypercalcemia. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Receiver operator characteristic curve thresholds for predicting severe hypocalcemia.

	Threshold[a]	Area under the curve	*p* value	Sensitivity	Specificity
Calcium to Blood Ratios, calcium administered (mmol) per blood product					
1–9 total transfusions	0.68	0.609	.141	56%	71%
10+ total transfusions	0.712	0.516	.673	59%	49%
All patients	0.712	0.564	.178	57%	57%
Calcium to Citrate Ratios, calcium administered (mmol) per FFP/PF24 equivalents of citrate					
1–9 total transfusions	1.13	0.585	.267	57%	67%
10+ total transfusions	1.31	0.510	.612	51%	54%
All patients	1.31	0.555	.225	53%	59%

Abbreviation: FFP/PF24, fresh frozen plasma and plasma frozen within 24 h.
[a]Optimal threshold between severely hypocalcemic patients and all other patients, as determined by a Receiver Operator Characteristic curve.

hypercalcemia was <0.903 mmol of administered calcium per blood product, which only had an AUC of 0.674, a sensitivity of 70%, and a specificity of 59%. The optimal ratio of calcium to blood or calcium to citrate administration to counteract citrate is yet to be determined and will require prospective studies.

TABLE 4 Receiver operator characteristic curve thresholds for predicting hypercalcemia.

	Threshold[a]	Area under the curve	*p* value	Sensitivity	Specificity
Calcium to Blood Ratios, calcium administered (mmol) per blood product					
1–9 total transfusions	1.46	0.762	.011	79%	72%
10+ total transfusions	0.955	0.691	<.001	61%	70%
All patients	0.903	0.674	.010	70%	59%
Calcium to Citrate Ratios, calcium administered (mmol) per FFP/PF24 equivalents of citrate					
1–9 total transfusions	2.27	0.754	.110	79%	69%
10+ total transfusions	1.44	0.689	<.001	68%	63%
All patients	1.44	0.658	.213	72%	58%

Abbreviation: FFP/PF24, fresh frozen plasma and plasma frozen within 24 h.
[a]Optimal threshold between hypercalcemic patients and all other patients, as determined by a Receiver Operator Characteristic curve.

TABLE 5 Quantile linear regression for continuous magnesium levels.

	0.25 quantile			0.5 quantile			0.75 quantile		
	β	SE	*p* value	*β*	SE	*p* value	*β*	SE	*p* value
All patients									
Presenting ER total magnesium, mmol/L	42.9	27.2	.140	46.2	27.1	.112	37.5	43.1	.400
Total blood products administered	−.062	0.028	.027	.0	0.079	>.999	.0	0.066	>.999
Total FFP/PF24 citrate equivalents administered	−.092	0.070	.191	.0	0.119	>.999	.0	0.178	>.999
Total 5% albumin administered (250 mL)	−1.37	0.405	.001	−0.822	0.679	.227	−.457	0.414	.271
Subgroup with total number of blood products ≥10									
Presenting ER total magnesium, mmol/L	60	27.9	.098	53.8	23.7	.085	43.8	19.2	.084
Total blood products administered	−.076	0.044	.084	.0	0.099	>.999	.0	0.159	>.999
Total FFP/PF24 citrate equivalents administered	−.123	0.060	.041	.0	0.126	>.999	.0	0.153	>.999
Total 5% albumin administered (250 mL)	−1.37	0.458	.003	−.822	0.921	.373	.0	0.757	>.999

Abbreviations: ER, emergency room; FFP/PF24, fresh frozen plasma and plasma frozen within 24 h; SE, bootstrapped standard error of regression coefficient; *β*, regression coefficient (mmol/L per 100 units of respective variable).

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CONFLICT OF INTEREST STATEMENT

Geoffrey Wool received honoraria and serves on advisory committees for Diagnostica Stago and HemoSonics. The authors have no other conflicts of interest.

ORCID

Husam Alghanem https://orcid.org/0000-0003-2817-0514
Chuanhong Liao https://orcid.org/0000-0002-4186-0520

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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