ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 2, Issue – 4, July - August - 2019, Page No. : 35 - 44

The Prognosticating Efficacy Of Corrected Calcium Level On Early, Late, And Overall 28-Day Mortality In Hypocalcemic Critically Ill Patients Who Are Taking Calcium Gluconate

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Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Objectives: Hypocalcemia is very common in critically ill patients admitted to ICU. However, its clinical importance and relation to the patient's clinical outcomes during the first week of admission is questionable. The aim of our study is to investigate the predictive efficacy of corrected calcium level (cCa) as tested prognosticator on early, late, and overall 28-day ICU mortality. Another aim of this study is to determine the optimal cCa in hypocalcemic critically ill patients who are taking calcium gluconate.

Methods: A retrospective analysis was conducted in our adult ICU at King Hussein Medical Hospital between April 2017 and Sep 2018. Chi square and Independent T-test were conducted to analyze the dichotomous and continuous variables A receiver operating characteristic (ROC) and sensitivity analysis were conducted to evaluate the prognostic ability and the optimal cutoff point of the cCa on the tested clinical outcomes.

Results: The early, late, and overall 28-day ICU mortality rate were 5.32% (10 patients), 35.12% (66 patients), and 40.4% (76 patients), respectively, in which the cCa was significantly higher in Survivors (8.14±0.24 mg/dl) compared to Nonsurvivors (7.91±0.29 mg/dl) and in late mortality (7.96±0.25 mg/dl) compared to early mortality (7.56±0.37 mg/dl). The best cut-off values for cCa for early, late, and overall 28-days ICU mortality in our study were 7.70 mg/dl, 8.09 mg/dl, and 8.09 mg/dl, respectively.

Conclusion: Hypocalcemia is associated with poor prognosis and higher mortality among critically ill patients, in addition to higher ICU and overall hospital length of stay. Calcium replacement to maintain cCa around 8 mg/dl does appear to improve mortality rates. cCa can be used as a predictor of prognosis in ICU patients.

Keywords: Calcium gluconate, Critically ill patients, Hypocalcemia, Mortality, Optimal corrected calcium level.

Introduction

Mortality is considered the worst clinical outcome in the Intensive Care Unit (ICU) setting. Early prediction of mortality in critically ill patients can help in the stratification of patients and give the best treatment accordingly. Therefore, predicting mortality risk is of great importance for ICU care. Several prognostic indices have been suggested as predictors of critically ill patient's mortality, but many of these suggested are too complicated to determine the mortality probability from. As a result, there has been an increasing necessity to establish a simplified mortality indicator while maintaining the prognostic accuracy and performance of the prognosticator.

Several studies had investigated the prognostic role of cCa in critically ill patients and its association with untoward clinical outcomes and/or mortality.[1] Derangements in calcium balance are common clinical problems with hypocalcemia prevalence reaching up to 88% of critically ill patients. The etiology of hypocalcemia among ICU patients is multifactorial, with several causes contributing to it, such as, abnormalities of The PTH-Vitamin D axis, medication side effects, as well as vitamin D deficiency due to a number of reasons, including the lack of sunlight, malnutrition, decreased renal 1-alpha-hydroxylation in acute renal failure and inflammatory response.[2,3,4]

Although many studies have demonstrated that hypocalcemia is correlated with the patient's severity of illness and mortality in the ICU, there is still no recommended priori target identified to which the administration of calcium should be titrated.[5] In this study, the predictive efficacy of cCa was investigated as a prognosticator on early (≤14 days), late (>14 days), and overall 28-day ICU mortality. Another aim of this study is to determine the optimal cCa in hypocalcemic critically ill patients who are taking calcium gluconate.

Material and Methods

This was a single-center observational retrospective study conducted in the departments of King Hussein Medical Center (KHMC) at Royal Medical Services (RMS) in Jordan. This study was approved by our Institutional Review Board (IRB), and a requirement for consent was waived owing to its retrospective design. This study included 188 hypocalcemic critically ill patients. Flow chart of our studied patient's selection and data collection process is fully illustrated in **Figure 1**.

Analysis values were compared for the two tested groups (Survivors vs Nonsurvivors) and the Nonsurvival group was further analyzed after being divided into 2 subgroups, early (≤14 days) and late (>14 days) mortalities. All patient's continuous variables were analyzed by using the Independent samples T-test to express them as Mean±SD in Survivors, early Nonsurvivors, late Nonsurvivors, and overall Nonsurvivors groups and to determine the Mean difference±SEM between comparable groups (Survivors vs Nonsurvivors and early Nonsurvivors vs late Nonsurvivors). One sample T-test was used to express the continuous variables as Mean±SD in all tested patients for comparable groups (Survivors vs Nonsurvivors) and in Nonsurvivors for comparable groups (early Nonsurvivors vs late Nonsurvivors). Categorical data were expressed as numbers with percentages by using the Chi square test. A ROC curve followed by sensitivity analysis was used to determine the area under the ROC curves (AUROCs), predictive performances, and the optimal cut-off values for cCa on the three tested mortalities. Youden indices, sensitivities, specificities, positive and negative predictive values, and accuracy indices were also calculated. Statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤0.05 were considered statistically significant.

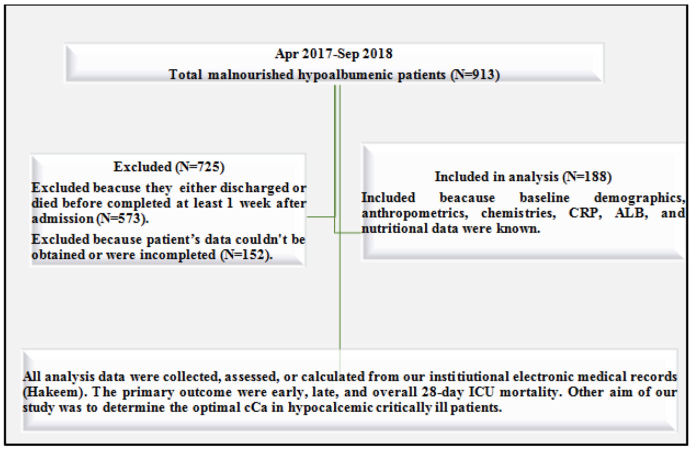

Fig 1. Flow chart of critically ill patient's selection and data collection process.

Apr: April. CRP: C-reactive protein. ICU: Intensive care unit.

Results

The mean age of our 188 studied hypomagnesemic critically ill patients was 58.94±10.4 years in which 131 patients (69.7%) of the eligible sample were male and 57 patients (30.3%) were female. The early, late, and overall 28-day ICU mortality rate were 5.32% (10 patients), 35.12% (66 patients), and 40.4% (76 patients), respectively, in which the cCa was significantly higher in Survivors (8.14±0.24 mg/dl) compared to Nonsurvivors (7.91±0.29 mg/dl) and in late mortality (7.96±0.25 mg/dl) compared to early mortality (7.56±0.37 mg/dl). The Survivors hypocalcemic critically ill patients who were administered Ca-Gluconate at dose of 1.97±0.25 g/day had significantly lower ICU and overall hospital LOS (9.29±1.14 days and 11.6±2.29 days) compared to Nonsurvivors hypocalcemic critically ill patients who were administered Ca-Gluconate at dose of 2.39±0.59 g/day (17.9±3.83 days and 25.2±1.41 days) with Mean differences±SEM of -8.58±0.39 days and -13.6±0.29 days, respectively. In case of Nonsurvivors, the late mortality hypocalcemic critically ill patients who were administered Ca-Gluconate at dose of 2.33±0.56 g/day had significantly higher ICU LOS but lower overall hospital LOS (19.2±1.76 days and 25.0±0.00 days) compared to early mortality hypocalcemic critically ill patients who were administered Ca-Gluconate at dose of 2.80±0.63 g/day (9.20±1.93 days and 26.4±3.84 days) with Mean differences±SEM of 9.98±0.61 days and -1.40±0.45 days, respectively. Demographics, admission co-morbidities and class, anthropometrics, and follow-up comparison data of the study's critically ill patients are fully summarised in **Table 1-2**.

Table 3 shows the optimal cut-off point, sensitivity (TPR), specificity (TNR), Youden index (YI), positive and negative predictive values (PPV and NPV), accuracy index (AI), and AUROC curve of cCa prognosticator for the three tested mortality groups (early, late and overall 28-days mortality). The best cut-off values for cCa for early, late, and overall 28-days ICU mortality in our study were 7.70 mg/dl, 8.09 mg/dl, and 8.09 mg/dl, respectively. The AUROCs of cCa prognosticator to predict the early, late, and overall 28-day ICU mortality in this study as fully illustrated in **Figures 2-4** were all significant with an AUC value of 0.871; 95% CI, 0.699-1.00 vs 0.834; 95% CI, 0.767-0.900 vs 0.893; 95% CI, 0.836-0.950, respectively.

Table 1. Baseline and follow-up comparison data of 28-day ICU survival and mortality for the study's hypocalcemic critically ill patients.

Variables	**Total (N=188)**	**Survivors (N=112)**	**Nonsurvivors (N=76)**	**Mean difference±SEM**	**P-Value**
Age (Yrs)	58.94±10.4	58.91±9.85	58.99±11.2	-0.08±1.55	0.961 (NS)

Gender	**Female**	57 (30.3%)	34 (30.4%)	23 (30.3%)		0.560 (NS)
	Male	131 (69.7%)	78 (69.6%)	53 (69.7%)		
BW (Kg)		74.05±10.2	75.27±10.4	72.25±9.79	3.02±1.51	0.047 (S)
BMI (Kg/m^2)		25.90±3.97	26.4±3.91	25.1±3.97	1.29±0.58	0.028 (S)
CRP (mg/dl)		13.19±4.27	11.3±2.39	15.9±4.93	-4.59±0.54	0.000 (S)
ALB (g/dl)		2.37±0.18	2.45±0.14	2.27±0.16	0.19±0.02	0.000 (S)
H.ALB (g/day)		20.00±0.00	20.0±0.00	20.0±0.00		NS
CRP: ALB		5.73±2.45	4.69±1.25	7.26±2.95	-2.57±0.31	0.000 (S)
TCR (Cal/kg/day)		9.49±0.75	9.83±0.59	9.00±0.67	0.83±0.09	0.000 (S)
TCR (Cal/day)		651.7±79.6	676.8±77.9	614.7±67.1	62.0±10.9	0.000 (S)
PD (g/100 Cal)		1.45±0.68	1.49±0.67	1.39±0.69	0.11±0.10	0.275 (NS)
SBP (mmHg)		105.6±12.9	111.8±3.15	96.4±16.1	15.4±1.56	0.000 (S)
DBP (mmHg)		60.34±13.2	66.7±3.20	51.0±16.5	15.6±1.59	0.000 (S)
MAP (mmHg)		75.70±12.1	81.8±3.15	66.8±14.7	15.0±1.43	0.000 (S)
BG (mg/dl)		188.7±6.72	185.5±3.52	193.4±7.51	-7.90±0.82	0.000 (S)
Ca (mg/dl)		6.77±0.33	6.92±0.23	6.55±0.34	0.38±0.04	0.000 (S)
cCa (mg/dl)		8.05±0.29	8.14±0.24	7.91±0.29	0.23±0.04	0.000 (S)
Calcium gluconate (g/day)		2.14±0.47	1.97±0.25	2.39±0.59	-0.42±0.06	0.000 (S)
Mg		1.90±0.20	1.99±0.09	1.77±0.24	0.23±0.03	0.000 (S)
Pre-ICU admission days		4.32±3.95	2.29±1.14	7.32±4.65	-5.03±0.46	0.000 (S)
ICU stay days		12.76±4.95	9.29±1.14	17.9±3.83	-8.58±0.39	0.000 (S)
Overall hospital stay days		17.07±6.98	11.6±2.29	25.2±1.41	-13.6±0.29	0.000 (S)
28-day ICU survival		112 (59.6%)				0.000 (S)
28-day ICU overall mortality		76 (40.4%)				

Values are presented as Mean±SD by using independent T-test and one sample T-test or as number (%) by using Chi-square test.

Group I: Patients who were on extended MgSO4 infusion strategy.

Group II: Patients who were on standard MgSO4 infusion strategy.

BW: Actual body weight.

CRP: C-reactive protein.

CRP:ALB ratio: C-reactive protein to albumin level ratio.

SBP: Systolic blood pressure.

DBP: Diastolic blood pressure.

BMI: Body mass index.

S: Significant (P-Value <0.05).

NS: Nonsignificant (P-Value >0.05).

N: Number of study's patients.

TCR: Total calories requirement.

PD: Protein density.

Δ: Changes occurred after the intervention.

ALB: Albumin level.

MAP: Mean arterial pressure.

BG: Blood glucose.

Ca: Total calcium level.

cCa: Corrected total calcium level.

Mg: Total magnesium level.

H.ALB: Human albumin 20%.

Table 2. Baseline and follow-up comparison data for early and late ICU mortalities of the study's hypocalcemic critically ill patients.

Variables		**Nonsurvivors (N=76)**	**Early mortality (≤14 days) (N=10)**	**Late mortality (>14 days) (N=66)**	**Mean difference±SEM**	**P-Value**
Age (Yrs)		58.99±11.2	62.7±6.98	58.4±11.6	4.28±3.78	0.262 (NS)
Gender	**Female**	23 (30.3%)	1 (10.0%)	22 (33.3%)		0.327 (NS)
	Male	53 (69.7%)	9 (90.0%)	44 (66.7%)		
BW (Kg)		72.25±9.79	73.408.69	72.1±10.0	1.32±3.34	0.693 (NS)
BMI (Kg/m^2)		25.1±3.97	25.1±4.71	25.1±3.89	-0.01±1.36	0.995 (NS)
CRP (mg/dl)		15.9±4.93	25.4±5.21	14.5±2.87	10.9±1.10	0.000 (S)
ALB (g/dl)		2.27±0.16	1.98±0.09	2.29±0.12	-0.32±0.04	0.000 (S)
CRP: ALB		7.26±2.95	12.9±3.47	6.39±1.59	6.61±0.65	0.000 (S)
TCR (Cal/kg/day)		9.00±0.67	7.90±0.32	9.17±0.54	-1.27±0.18	0.000 (S)
TCR (Cal/day)		614.7±67.1	554.1±35.3	623.9±66.1	-69.8±21.4	0.002 (S)
PD (g/100 Cal)		1.39±0.69	1.67±0.37	1.34±0.72	0.33±0.23	0.160 (NS)
SBP (mmHg)		96.4±16.1	62.5±20.7	101.5±6.09	-39.0±3.12	0.000 (S)
DBP (mmHg)		51.0±16.5	16.4±21.1	56.3±6.24	-39.9±3.19	0.000 (S)
MAP (mmHg)		66.8±14.7	35.2±16.1	71.5±6.09	-36.3±2.72	0.000 (S)
BG (mg/dl)		193.4±7.51	208.1±8.67	191.2±4.07	16.9±1.65	0.000 (S)
Ca (mg/dl)		6.55±0.34	5.99±0.51	6.63±0.21	-0.64±0.09	0.000 (S)
cCa (mg/dl)		7.91±0.29	7.56±0.37	7.96±0.25	-0.40±0.09	0.000 (S)
Calcium gluconate (g/day)		2.39±0.59	2.80±0.63	2.33±0.56	0.47±0.19	0.019 (S)
Mg		1.77±0.24	1.37±0.39	1.83±0.13	-0.46±0.06	0.000 (S)
Pre-ICU admission		7.32±4.65	17.2±5.73	5.82±1.76	11.4±0.88	0.000 (S)

days					
ICU stay days	17.9±3.83	9.20±1.93	19.2±1.76	-9.98±0.61	0.000 (S)
Overall hospital stay days	25.2±1.41	26.4±3.84	25.0±0.00	1.40±0.45	0.003 (S)
28-day ICU overall mortality	76 (40.4%)				0.000 (S)
Early mortality (≤14 days)	10 (5.32%)				
Late mortality (>14 days)	66 (35.12%)				

Values are presented as Mean±SD by using independent T-test and one sample T-test or as number (%)by using Chi-square test.

Group I: Patients who were on extended MgSO4 infusion strategy.
Group II: Patients who were on standard MgSO4 infusion strategy.
Yrs: Years.
Kg: Kilogram.
BW: Actual body weight.
BMI: Body mass index.
S: Significant (P-Value <0.05).
NS: Nonsignificant (P-Value >0.05).
N: Number of study's patients.
TCR: Total calories requirement.
PD: Protein density.
Δ: Changes occurred after the intervention.

CRP: C-reactive protein.
CRP:ALB ratio: C-reactive protein to albumin level ratio.
SBP: Systolic blood pressure.
DBP: Diastolic blood pressure.
MAP: Mean arterial pressure.
BG: Blood glucose.
Ca: Total calcium level.
cCa: Corrected total calcium level.
Mg: Total magnesium level.
ALB: Albumin level.
H.ALB: Human albumin 20%.

Discussion

In this retrospective study of 188 hypocalcemic, critically ill patients, we demonstrated that cCa was correlated with early, late, and 28-days overall mortality. The cCa was significantly higher in the group of patients who survived 28-days in the ICU (the period of the study) compared to patients who did not survive 28-days in the ICU (8.14±0.24 vs. 7.91±0.29). Furthermore, the stratification of Nonsurvivors into early-mortality and late-mortality groups has further confirmed the formerly mentioned correlation with cCa which was significantly higher in late-mortality group versus early-mortality group. (7.96±0.25 vs. 7.56±0.37). These results are consistent with previous evidence that described the strong relationship between lower cCa and increased mortality among critically ill patients.[5,6,7]

Table 3. The optimal cut-off point, sensitivity, specificity, positive and negative predictive values, Youden and accuracy indices, and expected early, late, and 28-day ICU mortality of cCa.

Prognostic Indicator		Optimal Cut-off	TPR	FPR	YI	TNR	PPV	NPV	AI	AUROC curve (95% CI)
cCa (mg/dl)	Overall 28-day mortality	8.09	94.70%	10.70%	84.00%	89.30%	85.73%	96.13%	91.48%	0.893 (0.836-0.950)
	Early mortality (≤ 14 days)	7.70	90.00%	5.10%	84.90%	94.90%	92.29%	93.33%	92.92%	0.871 (0.693-1.00)
	Late Mortality (> 14 days)	8.09	95.50%	17.20%	78.30%	82.80%	79.03%	96.44%	87.93%	0.834 (0.767-0.900)

cCa: Corrected total calcium level.
ICU: Intensive care unit.
TPR: True positive rate (sensitivity)
FPR: False positive rate.
YI: Youden index.
PPV: Positive predictive value.
NPV: Negative predictive value.
AI: Accuracy index.
TNR: True negative ratio (specificity).
AUROC: Area under receiver operating characteristic.

ROC Curve analysis of corrected calcium for overall 28-day ICU mortality

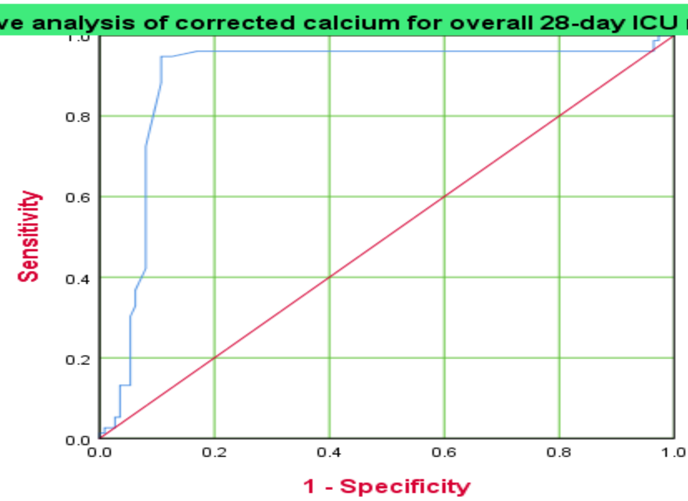

Figure 2. Receiver operating characteristic (ROC) curve analysis of corrected calcium prognosticator to determine the area under curve (AUC) and its predictive efficacy for overall 28-day ICU mortality in hypocalcemic critically ill patients who were taking calcium gluconate. The AUROC curve in our study was determined at 0.893 (95% CI, 0.836-0.950).

The major strength of this study is that we defined, for the first time, a cut-off cCa for hypocalcemia according to each time frame during ICU stay. The optimum cCa was found to be (7.7 mg/dl, 8.09 mg/dl, and 8.09 mg/dl) for early ≤14 days, late >14 days and 28-days of ICU stay, respectively. The Survivor patients who received calcium gluconate (1.97±0.25 g/day) had lower ICU LOS and hospital LOS compared to Nonsurvivors who were administered a higher dose of calcium gluconate (2.39±0.59 g/day). Calcium replacement appears not to improve mortality as long as the cCa is below the optimum levels as previously mentioned in other studies.[4] cCa must be a significant risk factor for mortality. However, this may not be reflected in a discriminative power of cCa for mortality prognosticating and a larger multisite, prospective study is needed to control for multiple confounders. This study is limited by its retrospective design and using single-center data. Nonetheless, our center is an experienced and high-volume unit, so our results may be useful to other centers.

ROC Curve analysis of corrected calcium for early ICU mortality

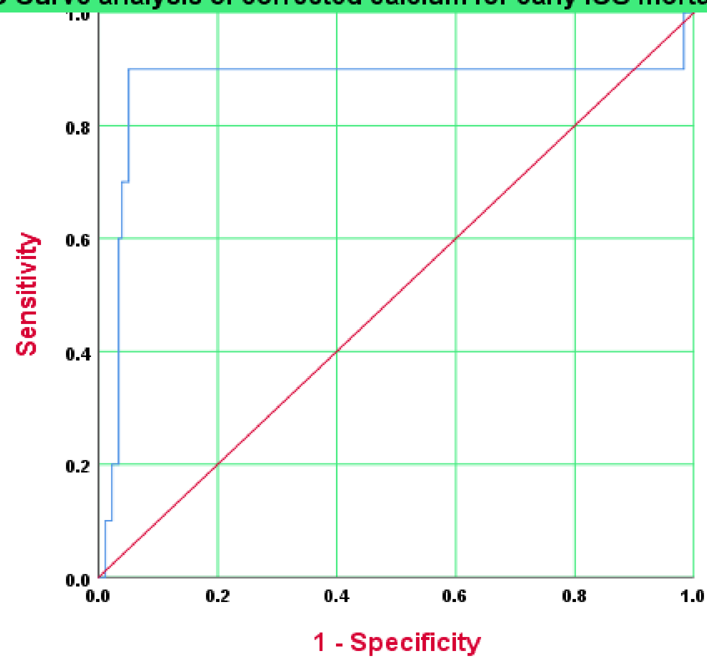

Figure 3. Receiver curve characteristic (ROC) cure analysis of corrected calcium prgnosticator to determine the area under curve (AUC) and its predictive efficacy for early ICU mortality in hypocalcemic critically ill patients who were taking calcium gluconate. The AUROC curve in our study was determined at 0.871 (95% CI, 0.693-1.00).

ROC Curve analysis of corrected calcium for late ICU mortality

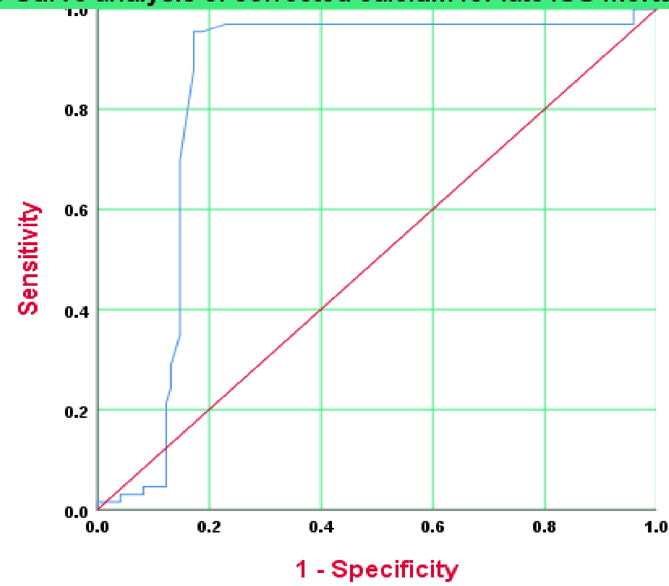

Figure 4. Receiver curve characteristic (ROC) curve analysis of corrected calcium prognosticator to determine the area under curve (AUC) and its predictive efficacy for late ICU mortality in hypocalcemic critically ill patients who were taking calcium gluconate. The AUROC curve in our study was determined at 0.834 (95% CI, 0.767-0.900).

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