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***Retrospective Study***

**Serum magnesium level as a predictor of acute kidney injury in patients with acute pancreatitis**

Yu XQ *et al*. Serum magnesium and AKI after AP

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**Abstract**

BACKGROUND

Decreased serum magnesium (Mg2+) is commonly seen in critically ill patients. Hypomagnesemia is significantly more frequent in patients with severe acute pancreatitis. Acute kidney injury (AKI) in patients with acute pancreatitis (AP) is associated with an extremely high mortality. The association underlying serum Mg2+ and AKI in AP has not been elucidated.

AIM

To explore the association between serum Mg2+ on admission and AKI in patients with AP.

METHODS

A retrospective observational study was conducted in a cohort of patients (*n* = 233) with AP without any renal injury before admission to our center from August 2015 to February 2019. Demographic characteristics on admission, severity score, laboratory values and in-hospital mortality were compared between patients with and without AKI.

RESULTS

A total of 233 patients were included for analysis, including 85 with AKI. Compared to patients without AKI, serum Mg2+ level was significantly lower in patients with AKI at admission [OR = 6.070, 95%CI: 3.374-10.921, *P* < 0.001]. Multivariate logistic analysis showed that lower serum Mg2+ was an independent risk factor for AKI [OR = 8.47, 95%CI: 3.02-23.72, *P* < 0.001].

CONCLUSION

Our analysis indicates that serum Mg2+ level at admission is independently associated with the development of AKI in patients with AP and may be a potential prognostic factor.

**Key Words:** Acute pancreatitis; Acute kidney injury; Magnesium (Mg2+); Kidney; Predictor of acute kidney injury

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**Core Tip:** Acute kidney injury (AKI) is a serious complication of acute pancreatitis (AP) and is often difficult to predict at an early stage. However, our clinical analysis found that serum Mg2+ on admission is a good predictor of the occurrence of AKI in AP patients. Therefore, this may provide a new method for the early prediction of AKI after AP.

**INTRODUCTION**

Acute pancreatitis (AP) is an autodigestive disease triggered by acinar cells, and about 20% of the patients progress to fatal severe acute pancreatitis (SAP)[1-4]. Acinar cell injury accompanied by intracellular electrolyte imbalance, further aggravating cell damage and even death is the recognized pathogenesis of AP[5,6]. In particular, organelle damage caused by intracellular calcium (Ca2+) influx into mitochondria is the main risk factor for AP[7]. An *in vitro* AP model showed that Ca2+ channel antagonists could effectively reduce Ca2+ influx and increase mitochondrial membrane potential, thereby protecting acinar cells[8,9]. As an important cation in cells, magnesium (Mg2+) is a coenzyme involved in a variety of enzymatic reactions and plays a role in maintaining membrane potential and physiological function[10-12]. In addition, Mg2+ plays a protective role in AP acinar cells by antagonizing Ca2+ signals[13]. On the contrary, abnormal regulation of Mg2+ acts as a pivotal trigger in the pathogenesis of AP[14].

Acute kidney injury (AKI) is a common complication of SAP with poor prognosis, especially when patients require renal replacement therapy, the mortality rate is > 75%[15,16]. SAP-associated AKI is related to systemic inflammatory response syndrome (SIRS), hypoxemia, renal microcirculation injury after trypsin release, renal perfusion pressure reduction caused by intraperitoneal high pressure or low blood volume, endotoxins and reactive oxides[17]. Therefore, early prediction of AKI in AP is very important to improve the course and prognosis of the disease.

AKI is often accompanied by complex electrolyte disturbances[18]. However, the relationship between Mg2+ and the occurrence of AP-associated AKI in AP pathophysiology has not been fully elucidated. Based on the beneficial role of Mg2+ in acinar cells of AP, we therefore sought to assess the value of serum Mg2+ on admission in correlation with the incidence of AKI in AP.

**MATERIALS AND METHODS**

***Patient selection***

We conducted a retrospective study of patients with AP admitted to the Center of Severe Acute Pancreatitis of Jinling Hospital between August 2015 and February 2019. All the data were extracted from an electronic database, which stored prospectively collected clinical data of all AP patients admitted to our center. We obtained the approval of the Acute Pancreatitis Database Management Committee (2018 JLAPDMC-009), and all the analyses were performed in accordance with the committee's regulations. Informed consent involving data storage and academic use of data was obtained from each patient during their hospitalization. Patients who met the following criteria were included: (1) Diagnosis of AP (ICD-10, K85) under the 2012 revision of the Atlanta classification; and (2) Admission to our department within one week after the disease onset. The exclusion criteria included any of the following: (1) The time from abdominal pain onset to hospital admission ≥ 7 d; (2) Age younger than 18 years; and (3) Suspected chronic pancreatitis, cancer, and chronic liver diseases such as cirrhosis or viral hepatitis, chronic kidney diseases such as nephritis, or renal failure. AKI (ICD-10: N17) was diagnosed according to the kidney disease: Improving Global Outcomes criteria based on serum/plasma creatinine and urine output. Patients meeting the diagnostic criteria for AP during hospitalization were included in the AKI group. The diagnosis of low serum Mg2+ was made by laboratory measurements on the day of admission.

***Data collection***

Demographic and baseline characteristics on admission included the following: Age, gender, body mass index (BMI), disease severity score (APACHE II), sequential organ failure assessment (SOFA), computed tomography severity index (CTSI), the Atlanta classification, comorbidities (diabetes, hypertension, hyperlipidemia), white blood cells, lymphocytes%, interleukin-6 (IL-6), procalcitonin (PCT), platelets, blood urea nitrogen (BUN), creatinine, HCO3-, and Cl-.

***Statistical analysis***

Statistical analysis was performed using R software, version 3.6.2 (R Foundation for Statistical Computing). The Kolmogorov-Smirnov test was used to test the normality. Continuous variables are presented as means and standard derivations or medians and interquartile ranges. Categorical variables are presented as number (frequency). The Mann-Whitney *U* test was used to evaluate the differences in baseline characteristics between the two groups. The Chi-square test or Fisher's exact test was used to analyze categorical variables for group comparisons. All variables with statistically significant prognostic value in univariate analysis were selected for further multivariate analysis. Odds ratio (OR) and 95% confidence intervals (CIs) are presented. Receiver operating characteristic curves were constructed to evaluate the sensitivity and specificity of serum Mg2+ in predicting AKI. *P* value < 0.05 was considered statistically significant.

**RESULTS**

***Baseline characteristics***

A total of 233 patients were included for analysis. The participant selection process is shown in Figure 1. The serum Mg2+ level of 0.755 mg/dL was identified as an effective cut-off point for in-hospital AKI occurrence (area under curve = 0.704; 95%CI: 0.640-0.775, *P* < 0.001), with a sensitivity of 77.7%, and specificity of 63.5% (Figure 2). Baseline characteristics of these patients are shown in Table 1. Compared with the non-low serum Mg2+ group, the group with low serum Mg2+ had higher BMI (*P* = 0.028) and APACHE II (*P* = 0.002). With regard to laboratory parameters, patients in the low serum Mg2+ group had higher admission IL-6 (*P* < 0.001), PCT (*P* < 0.001), and lower HCO3- (*P* < 0.001).

***Clinical outcomes***

The in-hospital clinical outcomes are shown in Table 2, divided according to admission serum Mg2+ level. The serum Mg2+< 0.755 mg/dL group consisted of 87 patients (54 cases in the AKI group and 33 cases in the non-AKI group), and the serum Mg2+ ≥ 0.755 mg/dL group consisted of 146 patients (31 cases in the AKI group and 115 cases in the non-AKI group). Lower serum Mg2+ was correlated with the occurrence of AKI (62.1% *vs* 21.2%, *P* < 0.001). The length of intensive care unit (ICU) stay (*P* < 0.001) and hospital stay (*P* < 0.001) of patients with low serum Mg2+ level was longer.

***Association of admission serum Mg2+ level with AKI occurrence***

As shown in Figure 3, compared with the non-AKI group, the AKI group had significantly lower serum Mg2+ level (*P* < 0.001). Following univariate logistic regression analysis, BMI (OR = 1.155, *P* < 0.001), APACHE II (OR=1.385, *P* < 0.001), SOFA (OR = 1.589, *P* < 0.001), CTSI (OR = 1.479, *P* < 0.001), severity classification (*P* < 0.001), IL-6 (OR = 1.006, *P* < 0.001), PCT (OR = 1.350, *P* < 0.001), BUN (OR = 1.368, *P* < 0.001), creatinine (OR = 1.051, *P* < 0.001), HCO3- (OR = 0.843, *P* < 0.001), and Cl- (OR = 1.100, *P* = 0.003) were important indicators of AKI in AP patients (Table 3). Multivariate logistic analysis showed that lower serum Mg2+ (OR = 5.525, *P* < 0.001) was an independent risk factor for AKI (Table 3).

**DISCUSSION**

In this research, we examined the involvement of serum Mg2+ and AKI in AP patients. Our results suggest that serum Mg2+ levels detected at admission were significantly lower in AP patients with AKI than in non-AKI patients. Moreover, the low serum Mg2+ group had a longer ICU and hospital stay than the non-low serum Mg2+ group. Furthermore, serum Mg2+ was revealed as an independent risk factor for the development of AKI. Therefore, serum Mg2+ is an effective predictor of AKI after AP.

Mg2+ is a well-known divalent cation abundant in human cells and is concentrated in mitochondria. It mainly plays the role of a cofactor in enzyme reactions and a second messenger in cellular signaling pathways[19-21]. In the physiological state of acinar cells, Mg2+ plays an antagonistic role in the influx of Ca2+ channel ions and inhibits the secretion of intracellular enzymes[9,22]. In the acinar cell model of AP, the addition of Mg2+ mitigates the effects of AP by inhibiting Ca2+ influx into the mitochondria, thereby reducing the secretion of digestive enzymes and promoting ATP generation[14]. In conclusion, Mg2+ plays an important regulatory role in the pathophysiological state of acinar cells. Mitochondria are the key organelles for the energy supply in acinar cells. It is obvious that Mg2+ plays an important role in maintaining mitochondrial homeostasis and ATP generation from this perspective.

The persistent influx of Ca2+ into the mitochondria of acinar cells in AP leads to increased oxygen radicals further triggering cell necrosis, which in turn induces SIRS[23-25]. This imbalance leads to further inflammatory response and oxygen radical production, resulting in multiple organ dysfunction including AKI[26]. Therefore, it is important to prevent the continuous influx of Ca2+ into mitochondria to reduce acinar cell necrosis and inhibit trypsin activation in AP. This is consistent with research in animal experiments[8,9]. In a murine model, the risk of triggering AP was decreased by inhibiting Ca2+ release-activated Ca2+ channels[27]. To the best of our knowledge, hypomagnesemia is commonly seen in severely ill patients including those with SAP[28]. In our SAP patients, there was a significant negative correlation between the incidence of AKI and adjusted serum Mg2+ on admission.

AKI as a complication, which is associated with increased mortality, occurs in approximately 15%-70% of SAP patients[18,29]. Therefore, early prediction of AKI in hospitalized patients with AP is imperative, especially for screening graded treatment strategies[30]. Currently, there are various clinical methods to predict the occurrence of AKI in patients with AP. On the whole, current studies on biomarkers for AP-associated AKI are insufficient, and the number of patients included in the analysis was limited. In addition, from the latest clinical evidence on the markers of AKI in AP, PCT showed relatively better clinical predictive value than neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C[31-33]. At present, serum or urine NGAL and serum cystatin C are recognized as the best laboratory indicators for predicting AKI in AP with good diagnostic accuracy. However, these single-center clinical data are not convincing enough. Large multicenter clinical studies on biomarkers are of great clinical value in identifying AKI in AP.

However, the relationship between admission serum Mg2+ level and AKI incidence in patients with AP has not been fully elucidated. Our results are the first to show that reduced serum Mg2+ levels are significantly associated with an increased risk of AKI in patients with AP. We found that Mg2+ level of 0.755 mg/dL was an effective cut-off point for in-hospital AKI occurrence, with a sensitivity of 77.7%, and specificity of 63.5%.

However, there are some limitations to our analysis. Firstly, our study did not consider the value of peripheral blood Mg2+; thus, the reliability of the actual level of free Mg2+ in peripheral blood may be significantly reduced from this perspective. Secondly, the causal relationship between Mg2+ and AP-associated AKI still needs to be verified by a large number of prospective studies. Thirdly, our analysis included only one checkup at admission, and as serum Mg2+ is a dynamic state, it may not fully reflect the true status of Mg2+ in these patients. From this perspective, dynamic serum Mg2+ measurement after admission is more objective in predicting AP-associated AKI. Finally, there may be methodological bias in our analysis, it is necessary to explore new machine models (such as train-validation models) to verify the current analysis results.

**CONCLUSION**

Our analysis indicates that serum Mg2+ level at admission is independently associated the development of AKI in patients with AP and may be a potential prognostic factor.

**ARTICLE HIGHLIGHTS**

***Research background***

There is a lack of effective predictors of acute kidney injury (AKI) after acute pancreatitis (AP) in clinical practice.

***Research motivation***

To investigate the association between serum Mg2+ on admission and AKI after AP.

***Research objectives***

To determine whether serum Mg2+ is a valid predictor of AP-associated AKI using clinical data from our severe acute pancreatitis center.

***Research methods***

Our center is one of the largest severe acute pancreatitis treatment centers in China. A total of 233 patients with AP from August 2015 to February 2019 were included in a retrospective analysis. Almost all clinical and laboratory indicators were included in the study.

***Research results***

Lower serum Mg2+ was correlated with the occurrence of AKI (62.1% *vs* 21.2%, *P* < 0.001). Patients in the low serum Mg2+ level group had a longer intensive care unit (*P* < 0.001) and hospital stay (*P* < 0.001).

***Research conclusions***

Serum Mg2+ on admission can effectively predict AKI in AP patients.

***Research perspectives***

This study provides ideas and a basis for prospective observation of AKI after AP, and provides early warning for effective intervention of the disease.

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**Footnotes**

**Institutional review board statement:** The study was reviewed and approved by the Nanjing Jinling Hospital Institutional Review Board.

**Informed consent statement:** All authors have agreed to publish this article.

**Conflict-of-interest statement:** The authors declare that they have no competing interests.

**Data sharing statement:** The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

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Grade A (Excellent): 0

Grade B (Very good): 0

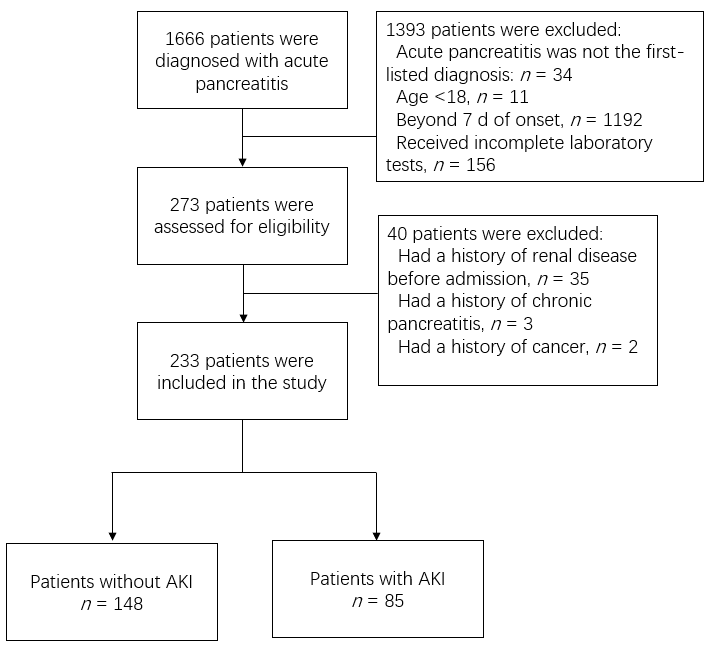
Grade C (Good): C

Grade D (Fair): 0

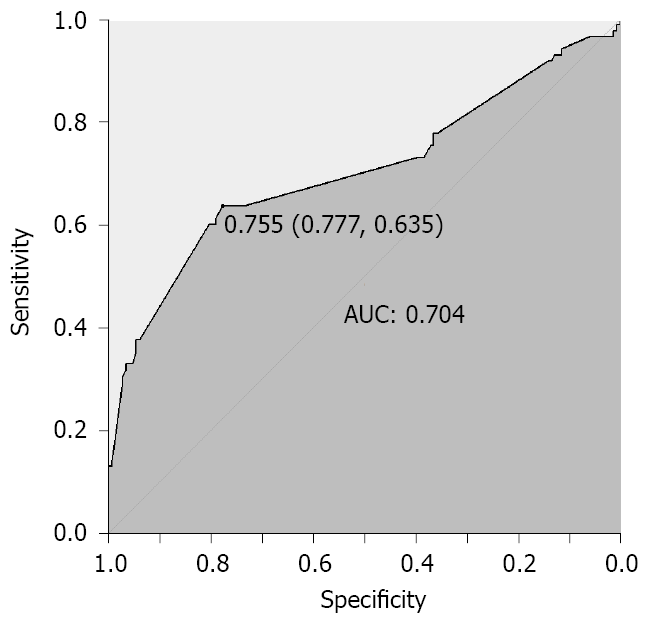
Grade E (Poor): 0

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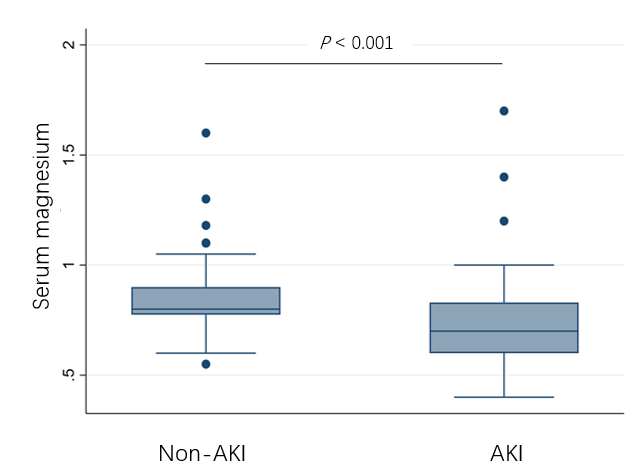
**Figure Legends**



**Figure 1 The flow diagram of patients.** A total of 1666 patients were included in the analysis. AKI: Acute kidney injury.



**Figure 2 Receiver operating characteristic curve for serum magnesium in predicting acute kidney injury.** AUC: Area under the curve.



**Figure 3 Serum magnesium in the acute kidney injury group versus the non-acute kidney injury group.** AKI: Acute kidney injury.

**Table 1 Baseline characteristics**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Mg2+ (mg/dL)** | | ***P* value** | **AKI, *n* = 85** | **Non-AKI, *n* = 148** | ***P* value** |
| **< 0.755 mg/dL, *n* = 87** | **≥ 0.755 mg/dL, *n* = 146** |
| Age, yr | 39 (32, 52) | 44 (34, 58) | 0.063 | 38 (30, 50) | 44.5 (35.5, 54.5) | 0.011 |
| Gender, male, *n* (%) | 59 (67.8) | 98 (67.1) | 0.913 | 59 (69.4) | 98 (66.2) | 0.913 |
| BMI | 27.1 (24.7, 30.1) | 25.6 (23.9, 28.1) | 0.028 | 27.6 (24.8, 30.7) | 25.4 (23.4, 27.7) | < 0.001 |
| APACHE II | 9 (7, 12) | 7 (5, 9) | 0.002 | 11 (8, 14) | 7 (4, 9) | < 0.001 |
| SOFA | 3 (3, 4) | 3 (2, 4) | 0.075 | 4 (3, 5) | 3 (2, 4) | < 0.001 |
| CTSI | 6 (3, 6) | 5 (3, 6) | 0.122 | 6 (6, 6) | 4 (2, 6) | < 0.001 |
| Severity classification, *n* (%) |  |  | 0.064 |  |  | < 0.001 |
| MAP | 21 (24.1) | 50 (34.2) |  | 7 (8.2) | 64 (43.2) |  |
| MSAP | 47 (54.0) | 79 (54.1) |  | 45 (53.0) | 81 (54.7) |  |
| SAP | 19 (21.8) | 17 (11.6) |  | 33 (38.8) | 3 (2.1) |  |
| Comorbidities |  |  |  |  |  |  |
| Diabetes | 23 (26.4) | 24 (16.4) | 0.066 | 20 (23.5) | 27 (18.2) | 0.066 |
| Hypertension | 22 (25.3) | 36 (24.7) | 0.914 | 22 (25.9) | 36 (24.3) | 0.914 |
| Hyperlipidemia | 25 (28.7) | 36 (24.7) | 0.493 | 21 (24.7) | 40 (27.0) | 0.493 |
| Laboratory data |  |  |  |  |  |  |
| WBC | 13.4 (10.6, 16.6) | 12.8 (10.1, 15.7) | 0.336 | 12.9 (10.9, 16.6) | 12.9 (10.3, 16.1) | 0.685 |
| Ly% | 8.1 (5.1, 11.2) | 6.7 (4.7, 10.6) | 0.297 | 6.9 (4.9, 10.5) | 7.2 (5, 11.2) | 0.769 |
| IL-6 | 199.6 (104.8, 366.4) | 115.4 (45.4, 201.5) | < 0.001 | 222.8 (130.4, 370) | 104.8 (45.4, 178.4) | < 0.001 |
| PCT | 1.2 (0.4, 3.3) | 0.4 (0.1, 1.6) | < 0.001 | 2.1 (1.1, 7.7) | 0.3 (0.1, 0.8) | < 0.001 |
| Platelets | 193 (142, 238) | 174 (134, 224) | 0.215 | 199 (132, 236) | 176.5 (142, 218) | 0.248 |
| BUN | 5.4 (3.7, 6.3) | 5.1 (4, 6.9) | 0.576 | 6 (4, 8.3) | 4.8 (3.8, 5.9) | < 0.001 |
| Creatinine | 61 (49, 8) | 63 (53, 8) | 0.924 | 50 (41, 57.3) | 51 (46, 59) | 0.184 |
| HCO3- | 18.9 (15.1, 23.5) | 22 (18.7, 24.2) | < 0.001 | 17.8 (13.7, 21.3) | 22.6 (19.8, 24.7) | < 0.001 |
| Cl- | 103 (99, 105) | 102 (100, 105) | 0.825 | 103.7 (101, 107) | 102 (99, 104) | < 0.001 |
| Mg2- |  |  |  | 0.7 (0.6, 0.7) | 0.885 (0.8, 0.9) | < 0.001 |

Mg2+: Magnesium; BMI: Body mass index; AKI: Acute kidney injury; SOFA: Sequential organ failure assessment; CTSI: CT severity index; MAP: Mild acute pancreatitis; MSAP: Mild severe acute pancreatitis; SAP: Severe acute pancreatitis; WBC: White blood cells; Ly%: Lymphocytes%; IL-6: Interleukin-6; PCT: Procalcitonin; BUN: Blood urea nitrogen.

**Table 2 Influence of low serum magnesium on clinical course**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Mg2+ (mg/dL)** | | | ***P* value** |
| **< 0.755 mg/dL, *n* = 87** | | **≥ 0.755 mg/dL, *n* = 146** |
| Primary outcome, *n* (%) |  |  | |  |
| AKI | 54 (62.1) | | 31 (21.2) | < 0.001 |
| Clinical course, days median |  |  | |  |
| ICU days | 3 (2, 6) | | 2 (1, 4) | < 0.001 |
| Hospital days | 6 (4, 10) | | 4 (3, 7) | < 0.001 |
| Severe outcome, *n* (%) |  |  | |  |
| ICU mortality | 1 (1.15) | | 3 (2.05) | 0.999 |
| 30 d mortality | 1 (1.15) | | 3 (2.05) | 0.999 |

Mg2+: Magnesium; AKI: Acute kidney injury; ICU: Intensive care unit.

**Table 3 Univariate predictors and multivariate model for acute kidney injury occurrence**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Univariate analysis** | **OR** | **95%CI** | ***P* value** | **Multivariate model** | **OR** | **95%CI** | ***P* value** |
| Mg2+ < 0.755, mg/dL | 6.070 | (3.374, 10.921) | < 0.001 | Mg2+ < 0.755, mg/dL | 5.525 | (2.074, 14.718) | < 0.001 |
| Age | 0.981 | (0.963, 1.000) | 0.052 | Age | 0.966 | (0.926, 1.007) | 0.104 |
| Gender | 1.158 | (0.652, 2.054) | 0.617 |  |  |  |  |
| BMI | 1.155 | (1.073, 1.244) | < 0.001 | BMI | 1.081 | (0.946, 1.236) | 0.251 |
| APACHE II | 1.385 | (1.256, 1.527) | < 0.001 | APACHE II | 1.130 | (0.976, 1.310) | 0.103 |
| SOFA | 1.589 | (1.307, 1.931) | < 0.001 | SOFA | 0.896 | (0.604, 1.330) | 0.585 |
| CTSI | 1.479 | (1.279, 1.711) | < 0.001 | CTSI | 1.107 | (0.815, 1.505) | 0.516 |
| Severity classification (MAP as reference) | | |  | Severity classification (MAP as reference) | | |  |
| MSAP | 4.870 | (2.071, 11.450) | < 0.001 | MSAP | 1.126 | (0.240, 5.289) | 0.880 |
| SAP | 84.857 | (23.269, 309.458) | < 0.001 | SAP | 15.260 | (1.817, 128.189) | 0.012 |
| Diabetes | 1.379 | (0.718, 2.647) | 0.334 |  |  |  |  |
| Hypertension | 1.086 | (0.588, 2.007) | 0.791 |  |  |  |  |
| Hyperlipidemia | 0.886 | (0.480, 1.634) | 0.698 |  |  |  |  |
| WBC | 1.026 | (0.970, 1.086) | 0.910 |  |  |  |  |
| Ly | 0.734 | (0.938, 1.046) | 0.734 |  |  |  |  |
| IL-6 | 1.006 | (1.004, 1.009) | < 0.001 | IL-6 | 1.003 | (0.999, 1.006) | 0.113 |
| PCT | 1.350 | (1.166, 1.562) | < 0.001 | PCT | 1.109 | (0.959, 1.283) | 0.163 |
| Platelets | 1.003 | (0.999, 1.007) | 0.139 |  |  |  |  |
| BUN | 1.368 | (1.196, 1.565) | < 0.001 | BUN | 1.102 | (0.826, 1.470) | 0.508 |
| Creatinine | 1.051 | (1.034, 1.069) | < 0.001 | Creatinine | 1.052 | (1.014, 1.091) | 0.006 |
| HCO3- | 0.843 | (0.794, 0.896) | < 0.001 | HCO3- | 0.993 | (0.894, 1.103) | 0.892 |
| Cl- | 1.100 | (1.032, 1.172) | 0.003 | Cl- | 1.042 | (0.936, 1.160) | 0.453 |

Mg2+: Magnesium; BMI: Body mass index; AKI: Acute kidney injury; SOFA: Sequential organ failure assessment; CTSI: CT severity index; MAP: Mild acute pancreatitis; MSAP: Mild severe acute pancreatitis; SAP: Severe acute pancreatitis; WBC: White blood cells; IL-6: Interleukin-6; PCT: Procalcitonin; BUN: Blood urea nitrogen; OR: Odds ratio; CI: Confidence interval.



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