Clin. Lab. 2022;68:XXX-XXX

ORIGINAL ARTICLE

Develop a Novel Nomogram to Predict Respiratory Failure in Acute Pancreatitis at Early Stage

Xinze Qiu, Fu Huang, Zhiyang Li, Xiaohe Wei, Jiangni Wu, Jiean Huang, Shiquan Liu

Department of Gastroenterology, The Second Affiliated Hospital of Guangxi Medical University, Guangxi, China

SUMMARY

Background: **Respiratory failure is a common complication in patients suffering from moderately severe or severe acute pancreatitis (AP). The aim of this study was to develop a novel nomogram to predict respiratory failure in AP early.**
Methods: **Patients, who were hospitalized within 72 hours of AP onset from January 1, 2018, to April 31, 2021 were enrolled in the study. The patients were divided into two groups including respiratory failure group and no respiratory failure group. The demographic characteristics and laboratory parameters were compared between the two groups. A nomogram was established with stepwise logistic regression and "rms" packages of R software.**
Results: **A total of 190 patients were finally included. White blood count, hemoglobin, sodium and calcium were significantly different between the two groups (all $p < 0.05$). White blood count (odds ratio [OR] = 1.28, 95% confidence interval [CI]: 1.14 - 1.47, $p < 0.001$), lymphocyte count (OR = 2.92, 95% CI: 1.16 - 7.70, $p = 0.023$), albumin (OR = 1.15, 95% CI: 1.01 - 1.33, $p = 0.045$) and calcium (OR = 0.00, 95% CI: 0.00 - 0.01, $p < 0.001$) were independent risk factors for respiratory failure in AP patients. After stepwise logistic regression was applied, white blood count, albumin, and calcium were used for the construction of the nomogram. The area under the curve (AUC) of the nomogram for respiratory failure was 0.832, which was higher than the BISAP score, and the nomogram possessed high concordance as calibration curves showed.**
Conclusions: **The nomogram could predict respiratory failure in AP at an early stage with high accuracy.**
(Clin. Lab. 2022;68:xx-xx. DOI: 10.7754/Clin.Lab.2021.210826)

Correspondence:
Shiquan Liu
Department of Gastroenterology
The Second Affiliated Hospital of
Guangxi Medical University
Nanning, Guangxi, 530007
P.R. China
Email: poempower@163.com

Manuscript accepted August 26, 2021

KEY WORDS

acute pancreatitis, respiratory failure, prediction, nomogram

INTRODUCTION

As one of the most common gastrointestinal diseases, the incidence of acute pancreatitis (AP) is 13 to 45 per 100,000 persons and is still increasing yearly worldwide [1]. It is known that acute pancreatitis is classified into three classifications including mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP) according to the Atlanta Classification. Even though the mortality of AP is not high at a rate of 1%, it cannot be ignored that SAP with multiple organ failure could lead to the death of 30% AP patients [2]. Respiratory failure is the most

common type of organ failure in AP patients and leads to poor prognosis in AP patients [3]. The patients suffering from AP with respiratory failure could benefit from early intervention. Hence, it is important to identify respiratory failure in AP patients at an early stage. Respiratory failure in AP is associated with inflammation and infection, but the mechanisms are still not well investigated [2]. Patients with respiratory failure usually are treated with respiratory therapy such as mechanical ventilation, low flow oxygen support and so on. Although the treatment has been improved, respiratory failure still occurs in AP patients in hospital frequently because of the lack of early prediction of respiratory failure. BISAP score, RANSON score, and APACHE II score are used to classify the severity of AP, but they could not predict respiratory failure properly. There are several studies which have identified the risk factors associated with respiratory failure in AP patients [4,5]. However, simple and accurate assessment methods still need to be established. In the present study, the risk factors of respiratory failure in AP were identified, and the nomogram was established based on the risk factors, which could be convenient to use in clinical practice.

MATERIALS AND METHODS

Patients

Patients with AP admitted to the Second Affiliated Hospital of Guangxi Medical University (Nanning City, Guangxi Province, China) from January 1, 2018, to April 31, 2021, were enrolled in the retrospective study. The diagnosis of AP was based on the revised 2012 Atlanta Criteria, which contain as least two criteria: (1) typical abdominal pain; (2) serum amylase or lipase is divided by the upper limit of normal ≥ 3 times; (3) imaging changes of contrast-enhanced computed tomography, magnetic resonance imaging or abdominal ultrasonography are consistent with AP [6]. Respiratory failure was diagnosed based on the modified Marshall scoring: $PaO_2/FiO_2 \leq 300$ mmHg. The patients were divided into two groups including respiratory failure group and no respiratory failure group.

The exclusion criteria were: (1) age < 18 years; (2) incomplete clinical information; (3) admitted more than 3 days after AP onset or treated in other medical institution; (4) patients with benign, malignant pancreatic tumors, autoimmune disease, or chronic disease (chronic obstructive pulmonary disease, chronic heart disease, chronic renal failure and so on).

Data collection

Baseline information was collected including age, gender, etiology, body mass index (BMI), the history of smoking and drinking, hospital stay, and hospital costs. Laboratory examination was collected within two days of admission. BISAP score was also evaluated with the worst condition within two days of admission.

Establishment of nomogram

To estimate the independent risk factors of respiratory failure in AP, univariate and multivariate logistic regression was used based on "glm" package. Furthermore, stepwise logistic regression model was used to extract the best predictive factors. The nomogram was constructed via the best predictive factors based on "rms" package. The discrimination and deviation of nomogram were assessed via receiver operating characteristic (ROC) curves and calibration curves, respectively.

Statistical analysis

All statistical analysis was performed using R software (version: 4.0.3). Fisher's exact test or χ^2 was used to compare categorical variables as appropriate, and Student's *t*-test or Mann-Whitney U test was used to compare continuous variables as appropriate. Comparison of area under curve (AUC) of ROC curves was performed using the Delong test. p-value < 0.05 was statistically significant.

RESULTS

Comparison of baseline information and laboratory examination

A total of 190 AP patients were included in the study, which contained 115 MAP, 49 MSAP, and 26 SAP. The patients were divided into two groups, 28 of whom were diagnosed with respiratory failure and 162 of whom were not. Demographic characteristics were compared between two groups (Table 1). There was no difference in age, gender, etiology, and the status of smoking and drinking between two groups, but BMI, hospital stay, and hospital costs of respiratory failure group were significantly higher than the no respiratory failure group. The baseline information between the two groups was comparable. Comparison of laboratory examination were shown in Table 2. The level of white blood count (WBC), percentage of neutrophils (Neu%), and hemoglobin (Hb) in the respiratory failure group were significantly higher than in the no respiratory failure group; sodium (Na^{2+}) and calcium (Ca^{2+}) in the respiratory failure group were significantly lower than the no respiratory failure group (all $p < 0.05$).

Logistic analyses of independent risk factors

Univariate and multivariate logistic analyses were applied to identify independent risk factors of respiratory failure in AP. The results showed that WBC, Hb, Na^{2+}, Ca^{2+}, and TG were statistically significant in the univariate analysis (all $p < 0.05$). In addition, after adjustment by multivariate logistic analyses, there were four independent risk factors including WBC (odds ratio [OR] = 1.28, 95% confidence interval [CI]: 1.14 - 1.47, $p < 0.001$), LC (OR = 2.92, 95% CI: 1.16 - 7.70, $p = 0.023$), ALB (OR = 1.15, 95% CI: 1.01 - 1.33, $p = 0.045$), and Ca^{2+} (OR = 0.00, 95% CI: 0.00 - 0.01, $p < 0.001$). For details, see Table 3. However, only WBC, ALB, and

Table 1. Comparison of baseline information among all patients.

Characteristic	No respiratory failure (n = 162)	Respiratory failure (n = 28)	p
Age (median [IQR])	44.00 [35.25, 57.75]	41.50 [35.50, 51.75]	0.522
Gender (%)			
Male	111 (68.5)	21 (75.0)	0.642
Female	51 (31.5)	7 (25.0)	
Etiology (%)			
Biliary	78 (48.1)	6 (21.4)	0.051
Alcoholic	20 (12.3)	4 (14.3)	
Hyperlipidemia	38 (23.5)	12 (42.9)	
Other cause	26 (16.0)	6 (21.4)	
BMI (median [IQR])	23.85 [21.73, 27.27]	25.44 [24.32, 27.58]	0.025
Smoking (%)			
No	95 (58.6)	14 (50.0)	0.518
Yes	67 (41.4)	14 (50.0)	
Drinking (%)			
No	96 (59.3)	14 (50.0)	0.478
Yes	66 (40.7)	14 (50.0)	
Hospital staying (median [IQR])	7.00 [5.00, 10.00]	15.00 [10.75, 20.00]	< 0.001
Hospital costs (median [IQR])	13,272.71 [8,900.52, 25,574.29]	36,650.40 [17,922.58, 58,369.89]	< 0.001

Table 2. Comparison of laboratory examination among all patients.

Characteristic	No respiratory failure (n = 162)	Respiratory failure (n = 28)	p
WBC (median [IQR])	11.59 [9.14, 14.43]	15.95 [12.77, 18.61]	< 0.001
PLT (median [IQR])	243.35 [195.15, 291.83]	255.35 [229.70, 315.70]	0.138
Neu% (median [IQR])	9.59 [7.13, 12.29]	12.65 [10.09, 16.45]	< 0.001
LC (median [IQR])	1.20 [0.79, 1.75]	1.34 [0.88, 1.98]	0.384
Hb (median [IQR])	143.40 [127.48, 155.07]	159.40 [143.95, 168.25]	0.001
MPV (median [IQR])	7.80 [7.01, 9.00]	7.63 [6.84, 8.43]	0.608
BUN (median [IQR])	3.95 [3.16, 5.61]	4.27 [3.56, 5.65]	0.176
Cr (median [IQR])	79.00 [65.00, 91.00]	82.00 [65.50, 93.50]	0.565
ALB (median [IQR])	42.05 [38.30, 44.77]	43.15 [37.30, 45.02]	0.755
AST (median [IQR])	33.00 [20.00, 118.00]	44.50 [23.75, 64.25]	0.364
ALT (median [IQR])	32.50 [16.25, 121.00]	34.00 [26.00, 66.50]	0.441
K^+ (median [IQR])	4.04 [3.71, 4.30]	4.15 [3.81, 4.46]	0.168
Na^+ (median [IQR])	138.70 [136.12, 140.78]	137.15 [134.75, 139.05]	0.017
Ca^{2+} (median [IQR])	2.25 [2.14, 2.32]	2.09 [1.85, 2.31]	0.024
TC (median [IQR])	4.34 [3.59, 5.89]	5.03 [3.73, 7.14]	0.462
TG (median [IQR])	1.27 [0.78, 4.53]	3.53 [0.83, 12.46]	0.080

Abbreviations: WBC - white blood count, PLT - platelets, Neu% - percentage of neutrophils, LC - lymphocyte count, Hb - hemoglobin, MPV - mean platelet volume, BUN - blood urea nitrogen, Cr - creatinine, ALB - albumin, AST - aspartate amino transferase, ALT - alanine amino-transferase, K^+ - potassium, Na^+ - sodium, Ca^{2+} - calcium, TC - total cholesterol, TG - triglyceride.

Table 3. Univariate and multivariate logistic regression analysis of clinical parameters.

Variables	Univariate analysis		Multivariate analysis	
	OR [95% CI]	p	OR [95% CI]	p
Age	0.99 [0.97, 1.02]	0.575	1.03 [0.99, 1.07]	0.212
Gender (male vs. female)	0.73 [0.27, 1.74]	0.493	2.31 [0.48, 11.77]	0.297
BMI	1.09 [0.99, 1.21]	0.089	1.06 [0.91, 1.25]	0.435
WBC	1.19 [1.10, 1.30]	< 0.001	1.28 [1.14, 1.47]	< 0.001
PLT	1.00 [1.00, 1.01]	0.189	1.00 [0.99, 1.01]	0.589
Neu%	3.38 [0.16, 81.99]	0.443	9.70 [0.06, 1,736.32]	0.385
LC	1.32 [0.79, 2.13]	0.266	2.92 [1.16, 7.70]	0.023
Hb	1.03 [1.01, 1.05]	0.004	1.01 [0.98, 1.05]	0.494
MPV	0.91 [0.66, 1.21]	0.527	1.03 [0.66, 1.56]	0.875
BUN	1.08 [0.92, 1.24]	0.288	0.98 [0.69, 1.36]	0.911
Cr	1.00 [0.99, 1.01]	0.657	1.00 [0.98, 1.02]	0.683
ALB	1.00 [0.93, 1.09]	0.911	1.15 [1.01, 1.33]	0.045
AST	1.00 [1.00, 1.00]	0.618	1.00 [0.99, 1.01]	0.848
ALT	1.00 [1.00, 1.00]	0.778	1.00 [0.99, 1.01]	0.970
K^+	1.96 [0.82, 4.70]	0.127	1.97 [0.54, 7.57]	0.309
Na^+	0.88 [0.78, 0.98]	0.023	1.04 [0.86, 1.27]	0.673
Ca^{2+}	0.02 [0.00, 0.14]	< 0.001	0.00 [0.00, 0.01]	< 0.001
TC	1.07 [0.90, 1.25]	0.427	0.99 [0.66, 1.39]	0.952
TG	1.07 [1.01, 1.14]	0.022	1.05 [0.92, 1.20]	0.493

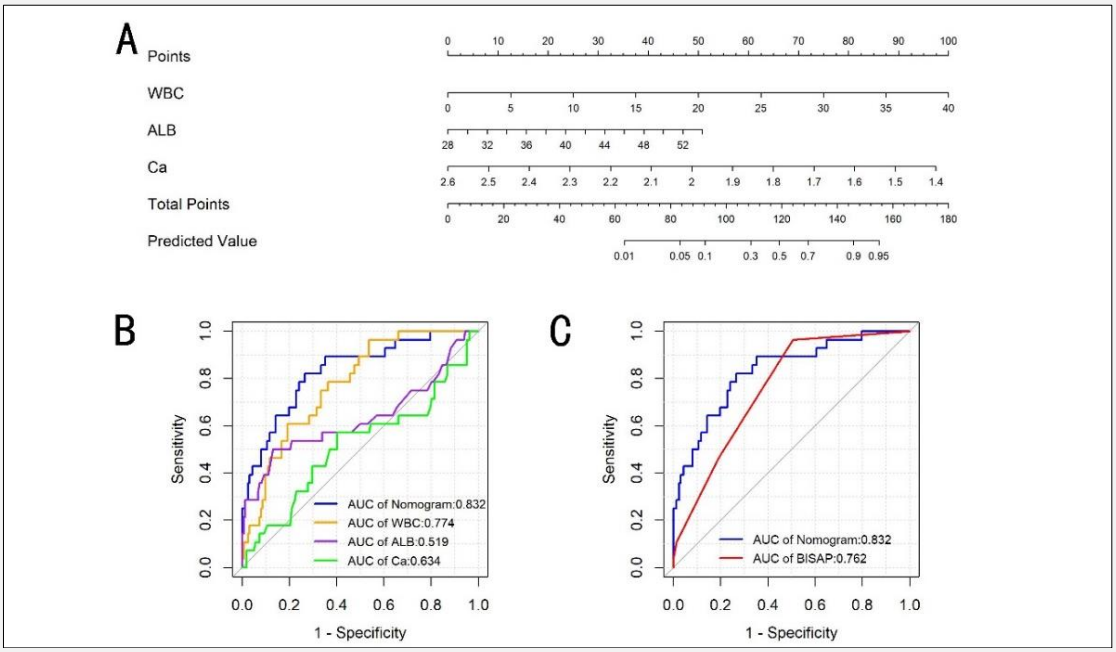

Figure 1. (A) Construction of nomogram for predicting the probability of respiratory failure in AP. (B) The comparison of the AUC between nomogram and single laboratory examination including WBC, ALB and Ca^{2+}. (C) The comparison of the AUC between nomogram and BISAP score.

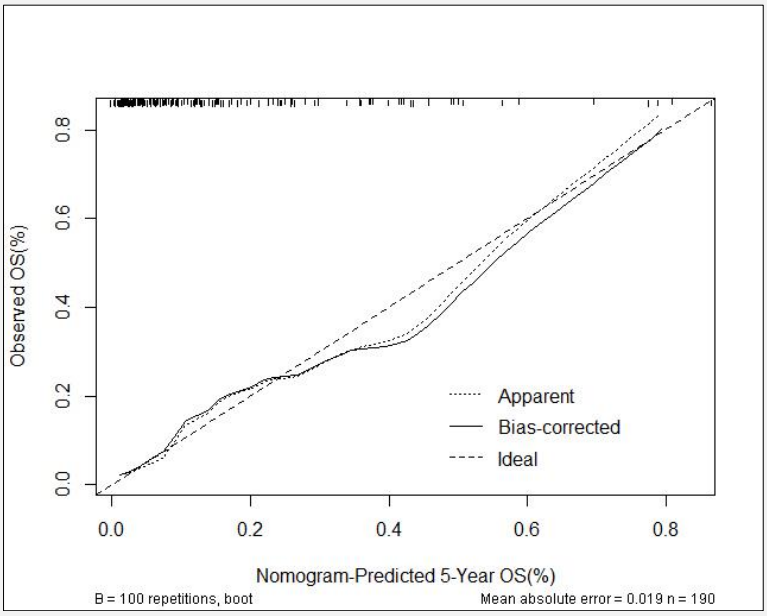

Figure 2. Calibration curves showed the accuracy of the nomogram in predicting respiratory failure in AP.

Ca^{2+} were finally screened out by stepwise multivariate logistic regression.

Development of nomogram

Subsequently, a nomogram was constructed with WBC, ALB, and Ca^{2+} (Figure 1A). ROC curve was applied to evaluate the discrimination of the nomogram. As Figure 1B showed, the AUC of the nomogram was 0.832 with a sensitivity of 82.1% and a specificity of 73.5% in the optimal threshold, which was larger than single laboratory examination including WBC (AUC = 0.774, $p = 0.237$), ALB (AUC = 0.519, $p < 0.001$), and Ca^{2+} (AUC = 0.634, $p < 0.001$). In addition, compared with the nomogram, the AUC of BISAP score (AUC = 0.762, $p = 0.009$) was smaller (Figure 1C). As the calibration curve showed, prediction using the nomogram was close to actual observation with a mean absolute error of 0.018 (Figure 2).

DISCUSSION

AP is a self-limiting disease, most patients without any organ failure have a benign prognosis [7]. Remarkably, there are still about 10 - 20% AP patients diagnosed as severe acute pancreatitis with organ failure, which leads to high mortality [8]. Besides, the study also reported that respiratory failure resulted in 60% deaths of AP patients [9]. So far, there is not proper method to predict the appearance of respiratory failure in AP. Therefore, it is urged to establish a novel method to identify respiratory failure in AP at an early stage.

In the current study, a novel nomogram was constructed to predict the probability of respiratory failure in AP, which includes three laboratory data: the level of WBC, ALB and Ca^{2+}. The nomogram possesses a good prediction ability as the ROC curves and calibration curves showed. Compared with the individual values, the nomogram had a larger AUC. Though there was no statistically significant difference between the nomogram and WBC, more samples could be adopted in subsequent analyses. The APACHE-II, Ranson, and BISAP scores are usually used to predict the severity of AP [10]. However, the APACHE-II score is too complex to be used in clinical practice frequently. The Ranson score needs at least 48 hours to evaluate the severity of AP, which might miss early intervention and lead to development of AP. The BISAP score is an easier score compared with APACHE-II score and Ranson score, and can predict the severity of AP in the first 24 hours after admission. Remarkably, it's not accurate enough to apply above the scores to predict respiratory failure in AP. In present study, the nomogram possessed larger AUC and less clinical parameters compared with BISAP score to predict respiratory failure in AP, which could greatly serve clinical practice.

WBC is a routine item in complete blood count, which has been regarded as a marker of inflammation and infection [11]. AP usually results in local necrosis and systemic inflammation. When inflammatory factors are

released, such as IL-1, IL-6, IL-8, TNF-a, white blood cells are active and aggregate, the permeability of pulmonary capillary endothelial cell membrane is increased, and this finally causes acute respiratory distress syndrome [12]. There were studies that also suggested that WBC could be used to distinguish the severity of AP [13,14]. In the current study, WBC showed moderate accuracy to predict respiratory failure in AP, which was consistent with previous studies. As is well known, ALB participates in the composition of colloid osmotic pressure. Hypoproteinemia could lead to pleural effusion, which might develop respiratory failure [15]. In addition, ALB is related negatively to inflammation reaction and organic oxidation resistance [16]. Studies have elucidated that inflammatory response induced by AP could increase the consumption and decrease the generation of ALB. Meantime, ALB is also a nutrition index, which is associated with poor prognosis in AP [17,18]. A study indicated that ALB could predict persistent organ failure with AUC of 0.873. The present study also suggested low level of ALB indicates worse prognosis [17]. Many studies have reported that serum Ca^{2+} is a risk factor for SAP [19,20]. However, the pathogenesis of hypocalcemia of AP patients remains unclear. Several studies suggest intracellular calcium overload could lead to the necrotic of the pancreas cells [21]. Meanwhile, the research also indicated that endotoxin was associated with hypocalcemia in AP, which might promote the transportation of calcium from the extracellular matrix [22]. Similar to other research, the present study also found hypocalcemia was associated with worse prognosis.

There are several limitations to the study. First, the present study was single-center and retrospective, the samples were relatively deficient. Due to this, verification of the model was absent. Second, other complications of AP were not included in the study such as renal failure, pancreatic pseudocysts, and so on. It might be interesting to investigate the correlation between respiratory failure and other complications.

CONCLUSION

In conclusion, the present study identified WBC, LC, ALB, and Ca^{2+} as independent risk factors in AP patients with respiratory failure. Based on only three laboratory examinations, a novel and simple nomogram was constructed, which could predict the probability of respiratory failure in AP at an early stage. The nomogram could be a useful tool in clinical practice and help clinicians to evaluate respiratory failure in AP early.

Acknowledgment:
None.

Declaration of Interest:
The authors declare that they have no potential conflicts of interest.

Data Availability Statement:
All the data released to this work are available at the corresponding author.

Source of Funds:
The present study was supported in part by the National Natural Science Foundation of China (No. 81460380), the Natural Science Foundation of Guangxi, China [2017GXNSFAA198019 and 2020GXNSFAA159056], and the Natural Science Foundation Fostering Science Foundation of the Second Affiliated Hospital of Guangxi Medical University, Guangxi, China [GJPY20180 10].

References:

1. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144(6):1252-61 (PMID: 23622135).
2. Garg PK, Singh VP. Organ Failure Due to Systemic Injury in Acute Pancreatitis. Gastroenterology 2019;156(7):2008-23 (PMID: 30768987).
3. Iyer H, Elhence A, Mittal S, Madan K, Garg PK. Pulmonary complications of acute pancreatitis. Expert Rev Respir Med 2020; 14(2):209-17 (PMID: 31779502).
4. Zhang W, Zhang M, Kuang Z, Huang Z, Gao L, Zhu J. The risk factors for acute respiratory distress syndrome in patients with severe acute pancreatitis: A retrospective analysis. Medicine (Baltimore) 2021;100(2):e23982 (PMID: 33466140).
5. Dombernowsky T, Kristensen MO, Rysgaard S, Gluud LL, Novovic S. Risk factors for and impact of respiratory failure on mortality in the early phase of acute pancreatitis. Pancreatology 2016; 16(5):756-60 (PMID: 27424478).
6. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62(1):102-11 (PMID: 23100216).
7. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet 2015;386(9988):85-96 (PMID: 25616312).
8. Hong W, Lillemoe KD, Pan S, et al. Development and validation of a risk prediction score for severe acute pancreatitis. J Transl Med 2019;17(1):146 (PMID: 31068202).
9. Banerjee AK, Haggie SJ, Jones RB, Basran GS. Respiratory failure in acute pancreatitis. Postgrad Med J 1995;71(836):327-30 (PMID: 7644392).
10. Papachristou GI, Muddana V, Yadav D, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. Am J Gastroenterol 2010;105(2):435-41; quiz 442 (PMID: 19861 954).

11. Farkas N, Hanak L, Miko A, et al. A Multicenter, International Cohort Analysis of 1,435 Cases to Support Clinical Trial Design in Acute Pancreatitis. Front Physiol 2019;10:1092 (PMID: 31551798).

12. Preira P, Forel JM, Robert P, et al. The leukocyte-stiffening property of plasma in early acute respiratory distress syndrome (ARDS) revealed by a microfluidic single-cell study: the role of cytokines and protection with antibodies. Crit Care 2016;20:8 (PMID: 26757701).

13. Szabo FK, Hornung L, Oparaji JA, et al. A prognostic tool to predict severe acute pancreatitis in pediatrics. Pancreatology 2016; 16(3):358-64 (PMID: 27051062).

14. Wang Y, Xu Z, Zhou Y, et al. Leukocyte cell population data from the blood cell analyzer as a predictive marker for severity of acute pancreatitis. J Clin Lab Anal 2021;35(7):e23863 (PMID: 34062621).

15. Akkurt I, Copur AS, Samurkasoglu AB, Ugur P, Sayfikli Z. The serum-effusion albumin gradient in the evaluation of pleural effusions. Chest 1993;103(5):1634-5 (PMID: 8329072).

16. Arroyo V, Garcia-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014;61(2): 396-407 (PMID: 24751830).

17. Li S, Zhang Y, Li M, Xie C, Wu H. Serum albumin, a good indicator of persistent organ failure in acute pancreatitis. BMC Gastroenterol 2017;17(1):59 (PMID: 28446147).

18. Hong W, Lin S, Zippi M, et al. Serum Albumin Is Independently Associated with Persistent Organ Failure in Acute Pancreatitis. Can J Gastroenterol Hepatol 2017;2017:5297143 (PMID: 29147647).

19. Yu S, Wu D, Jin K, et al. Low Serum Ionized Calcium, Elevated High-Sensitivity C-Reactive Protein, Neutrophil-Lymphocyte Ratio, and Body Mass Index (BMI) Are Risk Factors for Severe Acute Pancreatitis in Patients with Hypertriglyceridemia Pancreatitis. Med Sci Monit 2019;25:6097-103 (PMID: 31413252).

20. Gravito-Soares M, Gravito-Soares E, Gomes D, Almeida N, Tome L. Red cell distribution width and red cell distribution width to total serum calcium ratio as major predictors of severity and mortality in acute pancreatitis. BMC Gastroenterol 2018; 18(1):108 (PMID: 29976140).

21. Petersen OH, Gerasimenko JV, Gerasimenko OV, Gryshchenko O, Peng S. The roles of calcium and ATP in the physiology and pathology of the exocrine pancreas. Physiol Rev 2021;101(4): 1691-744 (PMID: 33949875).

22. Ammori BJ, Barclay GR, Larvin M, McMahon MJ. Hypocalcemia in patients with acute pancreatitis: a putative role for systemic endotoxin exposure. Pancreas 2003;26(3):213-7 (PMID: 12657944).