A Simple Clinical Classification System for Early Definitive Treatment Improves Quality of Care in Acute Biliary Pancreatitis

Shengjie Dai

wenzhou medical collage

Hongru Kong

Wenzhou Medical College First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Meng Wang

Wenzhou Medical College First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Zhe Chen

Wenzhou Medical College First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Huajun Yu

Wenzhou Medical College First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Yuepeng Jin

Wenzhou Medical College First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Yunfeng Shan

Wenzhou medical collage

Keqing Shi

wenzhou medical collage

Hong-Wei Sun (✉ sunhongwei1@163.com)

The First Affiliated Hospital of Wenzhou Medical University <https://orcid.org/0000-0001-5700-8247>

Research

Keywords: acute biliary pancreatitis, clinical classification, common bile duct stones, systemic inflammatory response syndrome, mortality

Posted Date: November 5th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-101273/v1>

Abstract

Background

The complexity of acute biliary pancreatitis (ABP) regarding severity of pancreatitis, accompanying diseases in the biliary system, and the variety of available interventions have raised the need for individualized treatment. We aimed to develop a simple clinical classification system guiding early and definitive treatment in patients with ABP to improve quality of care.

Methods

The classification system for ABP was developed according to severity of disease, biliary obstruction, and common bile duct stone. 2951 patients (retrospective cohort) collected between June 2006 and July 2017 and 323 patients (prospective cohort, guided by the classification system) collected between August 2017 and May 2018 were used to compare quality of care: rate of early-definitive treatment and mortality.

Results

ABP patients were divided into four classes: Type I, non-obstructive mild ABP; Type II, obstructive mild ABP; Type III, obstructive moderately severe/severe ABP; Type IV, non-obstructive moderately severe/severe ABP; each type was distributed into two subtypes: subtype a, accompanied by common bile duct stones; subtype b, without common bile duct stones. With the guidance by the classification system, the rate of early definitive treatments increased in Type I/II. Continuous regional arterial infusion was recommended as an early definitive treatment for patients with Type III/IV, in which the mortality has clearly descended.

Conclusions

For patients with ABP, we present a simple clinical classification system with 4 distinct types, with 2 subtypes for guiding the early-definitive treatment for ABP.

Introduction

Acute pancreatitis (AP), a sudden inflammatory process in the pancreas, is one of the most common gastrointestinal emergency conditions that are associated with substantial suffering, morbidity, and cost to the health care system^{1,2}. An increase in incidence of AP has been noted during recent years³. In case of severe acute pancreatitis (SAP), the acute inflammatory response may progress to a systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS), with a potential lethal outcome^{4–6}.

The management of AP is an enormous challenge for clinicians. Assessment and classification of the disease severity are the first facet so that clinicians can recognize, anticipate, and treat complications

accordingly. The revised 2012 Atlanta criteria stratified the severity of AP into three categories: mild, moderately severe, and severe, which are widely accepted⁷. The second facet to management of AP is to identify the etiology and remove it⁵. Gallstone disease is one of the main causes of AP, accounting for 40% of AP hospitalizations⁸. Temporary obstruction caused by gallstones at the ampulla of Vater results in increased pressure and activates enzyme within the pancreas, leading to onset of acute biliary pancreatitis (ABP)^{8,9}. Due to common bile duct stones (CBDS), ABP may be complicated with e.g. jaundice and infection^{10,11}. Therefore, ABP is a complex disease referring to the biliary pathogenesis and the pancreatic inflammation, which affect the severity, complication rate and prognosis.

Guidelines recommend definitive treatment of the gallstones (cholecystectomy or endoscopic sphincterotomy) to be performed in patients with mild ABP during the same hospital admission or within 2 weeks of discharge^{5,12–14}. For those with moderately/severe ABP, the initial management is supportive care and management of complications¹⁵. The delayed cholecystectomy may allow the inflammation to settle down completely^{16,17}. Overall hospital stay length and further episodes of AP can be reduced in these patients who adherent to the guidelines¹⁸.

Therefore, clear diagnosis and severity stratification of ABP are crucial for early-definitive intervention by which quality of care, such as mortality, surgical complication rates and readmission rates in ABP could be improved. In the current study, we established a simple clinical classification system for ABP according to biliary pathogenesis and severity of the disease. Then, the system was evaluated for its use in aiding clinical evaluation and guiding early-definitive treatment.

Methods

Study Design and Population

The principles of the simple clinical classification system for ABP include the following characteristics: (1) the severity of AP stratified by the revised 2012 Atlanta criteria is the standard classification of the severity of AP⁷; (2) biliary obstruction or not, which is associated with the patterns of interventions; (3) whether there is CBDS. The ABP patients were retrospectively collected between June 2006 and July 2017 in the First Affiliated Hospital of Wenzhou Medical University (retrospective cohort), which were treated without using the classification system. Then, the classification system was prospectively implemented in patients with ABP enrolled between August 2017 and May 2018 in the First Affiliated Hospital of Wenzhou Medical University (prospective cohort). The early definitive treatment rate and mortality were compared in both cohorts for the classification system use in guiding definitive treatment. The research protocol of the study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (Ethics number: 2017-197). The study was registered in the Chinese Clinical Trial Registry (ChiCTR-OOC-17013097).

Inclusion and exclusion criteria

All enrolled patients met the criteria for ABP, the diagnosis of which was made within the setting of ongoing abdominal pain, hyperamylasemia (of >3 times the normal), elevated liver enzymes, hyperbilirubinemia (of >2mg/dL) and gallstones/sludge within the gallbladder or the bile duct⁸. Patients who met the following criteria were excluded: (1) Other etiologies of AP, (2) Recurrent, not first-time pancreatitis or chronic pancreatitis, (3) Previous pancreatic surgery or injury, (4) Pancreatic cancer or other malignant tumors, (5) Pregnancy/pediatric population, (6) Refusal of cholecystectomy or endoscopic sphincterotomy or intolerance of operation, (7) Patients without available data.

Definitions

The severity of AP stratified as mild AP or moderate/severe AP according to the revised 2012 Atlanta criteria. A biliary obstruction was defined as a biliary obstruction sign: 1) dilated common bile duct on imaging (defined as > 8 mm in patients aged $\leq$ 75 years and > 10 mm in patients aged > 75 years) or jaundice. Organ failure was defined as having a Marshall score $\geq$ 2 for at least one of the three organs (respiratory, cardiovascular, and renal failure) involved¹⁹. Our primary outcome was to determine the effect of the clinical classification system on the quality of care, including early definitive treatment, and in-hospital mortality in ABP. Early definitive treatment of the gallstones was considered as cholecystectomy or endoscopic sphincterotomy during the same hospital admission or within 2 weeks of discharge in accordance with the guidelines. Once the patients were diagnosed as a moderate severe ABP, continuous regional arterial infusion (CRAI) was started in addition to supportive care and management of complications^{20,21}.

Clinical information and laboratory examinations

A detailed history of all the patients was taken. Baseline patient characteristics were collected within the first 24 hours after the established diagnosis of ABP, including age, sex, vital signs, physical exam findings, serum levels of aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, direct bilirubin, lactate dehydrogenase, amylase, lipase, C-reactive protein, blood urea nitrogen (BUN) and white blood cells (WBC).

SIRS was defined by the presence of $\geq$ 2 of the following criteria: pulse >90 beats/min,

respiration rate >20 per min, or PaCO₂ < 32 mm Hg, temperature >38 °C or < 36°C and white blood cell count >12,000 or < 4,000 cells per mm³ or >10 % immature neutrophils. The bedside index for severity in AP (BISAP) uses five points: BUN >25 mg / dl, impaired mental status by evidence of disorientation or disturbance in mental status, presence of the SIRS, age >60 years, and pleural effusions²². Common bile duct stones were detected by trans-abdominal ultrasound scanning, magnetic resonance cholangiopancreatography, or endoscopic ultrasound.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation or median and interquartile range (IQR) depending on the variable distribution; and categorical values were expressed by absolute and relative frequencies. The significance of the difference between 2 independent samples were analyzed using Student t-tests or Mann-Whitney U test. The Chi-square test was used for categorical data. P value <0.05 was considered statistically significant. Statistical analysis was conducted by SPSS 22.0 (SPSS, Chicago, IL).

Results

Clinical classification system for ABP

After a discussion, along with a review of several guidelines for management of AP and gallstone disease, it was agreed that the clinical classification system should provide criteria to differentiate types of ABP (disease severity, biliary obstruction, and common bile duct stones) and to make any kind of sensible decision about which treatment is best. According to the severity of AP and biliary tract obstruction or not, ABP patients were divided into four classes: Type I, non-obstructive mild ABP; Type II, obstructive mild ABP; Type III, obstructive moderately severe/severe ABP; Type IV, non-obstructive moderately severe/severe ABP; each type was distributed into two subtypes: subtype a, accompanied by common bile duct stones; subtype b, without common bile duct stones (Figure 1). The schematic diagram of the classification system was shown in Figure 2. For example, an ABP patient who had mild ABP with biliary obstruction and accompanied by common bile duct stones would be assigned to Type II-a by the classification system.

Selection and characteristics of patients with ABP

Study design and flowchart of patient selection were shown in Figure 3. From June 2006 and July 2017, 7270 patients were identified due to an admission for AP in the retrospective cohort. A total of 4319 patients were excluded from the study, leaving 2951 patients with ABP for evaluating the classification system. Between August 2017 and May 2018, 323 patients with ABP were classified in the prospective cohort. There were 69 patients in the retrospective cohort and 4 patients in the prospective cohort that died ($P = 0.317$). The baseline characteristics of the two cohorts of patients were listed in Table 1. The condition of the patients in the retrospective cohort was similar as in the prospective cohort, except for alanine aminotransferase ($P < 0.001$), aspartate aminotransferase ($P < 0.001$) and WBC ($P = 0.007$). The proportion of moderately severe or severe ABP was higher in the prospective cohort than in the retrospective cohort (30.0% prospective cohort vs. 13.4% retrospective cohort, $P \leq 0.001$), lining in BISAP score (1.17 ± 0.97 prospective cohort vs. 0.83 ± 0.85 retrospective cohort, $P \leq 0.001$) and hospital stays (median 15 prospective cohort vs. 11 retrospective cohort, $P \leq 0.001$).

Evaluation of the classification system

In the retrospective cohort, moderately severe/severe ABP occurred in 354 (13.4%) patients, 799 (27.1%) patients with biliary tract obstruction, 888 (30.1%) patients with common bile duct stones, and 666

(22.6%) patients with SIRS. According to the classification system, 1876 (63.6%) patients were assigned to Type I, with subtype a 277 (9.4%) and subtype b 1599 (54.2%). Type II consisted of 681 patients (subtype a, 497, 16.8%; subtype b, 184, 6.2%). In total, 118 (4.0%) patients and 276 (9.4%) patients were allocated to Type III and Type IV, respectively. In the prospective cohort, the distribution of each type was similar as compared to the retrospective cohort.

The characteristics of each type in the retrospective and prospective cohorts are shown in Table 2 and Table 3, respectively. In both cohorts, the patients with Type III/IV had higher BISAP score than patients with Type I/II (Figure 4). Risk factors indicating moderately severe/severe ABP, such as albumin, serum calcium, C reactive protein, and pleural effusion were also identified in patients with Type III/IV. Moreover, the present of SIRS and the proportion of two or more positive SIRS criteria increased in Type III/IV (Figure 5).

Classification system guiding treatment for ABP

In the prospective cohort, the classification system was implemented for guiding the treatment of ABP. A total of 175 (77.4%) patients with Type I/II received early-definitive treatment; 101 had a cholecystectomy, 54 had an endoscopic sphincterotomy, 12 had both procedures, and 4 had choledocholithotomy. For Type I-a, cholecystectomy and endoscopic sphincterotomy were main procedures; cholecystectomy mainly for Type I-b. Due to biliary obstruction, endoscopic sphincterotomy was mainly performed in patients with Type II (Table 4). The proportion of patients with Type I/II receiving early definitive treatment was improved with the guidance of the classification system (77.4% prospective cohort vs. 35.9% retrospective cohort, $P < 0.001$), which was also done in each subtype (Figure 6).

In Type III/IV, 84 (86.6%) patients had a continuous regional arterial infusion once assigned to these two types. Choledocholithotomy, or endoscopic sphincterotomy was conducted in 10 (90.9%) patients with Type III-a due to biliary obstruction combined with common bile duct stones (Table 5). Four (4.1%) patients died, while the mortality among Type III/IV in the retrospective cohort was 15.2% ($P < 0.001$). Detailed mortality of each subtype was illustrated in Figure 7.

Discussion

ABP is characterized by inflammation of the pancreas and biliary pathogenesis that can result in MODS and death. Considering severity, complication and prognosis, identification of different morbid states in ABP should be developed. In the current study, we have derived a simple clinical classification system for use in ABP. Using disease severity (revised 2012 Atlanta criteria), biliary obstruction, and common bile duct stones, the novel classification system was able to stratify patients within the first 48 h of hospitalization into 4 distinct types with 2 subtypes for guiding the early-definitive treatment for ABP.

Patients with moderately SAP or with SAP have distinct risks for in-hospital mortality. Therefore, as a first step, the severity of ABP (divided into Type I/II or Type III/IV) should be determined by the classification system. The mortality was 0.3% and 15.2% in Type I/II and Type III/IV in the retrospective cohort,

respectively ($P = 0.001$); 0% and 4.1% in the prospective cohort, respectively ($P = 0.008$). Since the pattern of surgery in turn depends on biliary obstruction, it is critical for introducing biliary obstruction into the classification system. Therefore, ABP was stratified as 4 distinct types by the classification system: non-obstructive mild ABP, obstructive mild ABP, non-obstructive moderately severe/severe ABP, obstructive moderately severe/severe ABP. Common bile duct stone is the main cause of biliary obstruction. In a few patients, persistent CBDS could lead to ongoing pancreatic duct or bile duct obstructions, in turn leading to SAP. Nevertheless, in some cases, biliary obstruction might be caused by postoperative strictures, inflammatory changes in the pancreas, ampulla or bile ducts and traumas⁸. Furthermore, CBDS does not always lead to biliary obstruction. In the retrospective cohort of 799 patients with biliary obstruction, 232 (29.0%) patients had no common bile duct stone; 65.2% patients with biliary obstruction had common bile duct stone in the prospective cohort. Therefore, it was important to figure out the association between biliary obstruction and CBDS. Subtype a or b in each type represented as CBDS or non-CBDS should be addressed.

For the convenience of the classification system in clinical application, 4 distinct types were sorted by the severity and prognosis of ABP: Type I, Type II, Type III, and Type IV. Patients with non-obstructive mild ABP or obstructive mild ABP frequently recover within about 7 days of onset of illness. However, patients with pancreatitis who have persistent biliary obstruction are recommended to undergo urgent biliary sphincterotomy and endoscopic stone extraction. Otherwise it is possible to aggravate the state of illness by biliary obstruction. Non-obstructive mild ABP and obstructive mild ABP were therefore defined as Type I and Type II, respectively. In addition, all deaths in the prospective cohort occurred in patients with non-obstructive moderately severe/severe ABP with the standard care provided according to guidelines. Obstructive moderately severe/severe ABP and non-obstructive moderately severe/severe ABP were therefore defined as Type III and Type IV, respectively. As a prognostic scoring system for use in AP, BISAP score was higher in patients with Type III/IV than that in patients with Type I/II. A few parameters that were associated with increased mortality in AP, such as albumin²³, serum calcium²⁴, C reactive protein²⁵, and pleural effusion²⁶ also displayed a marked difference between Type I/II and Type III/IV. Moreover, the presence of SIRS and the proportion of two or more positive SIRS criteria increased in Type III/IV. SIRS which has become increasingly widespread in clinical practice for evaluation of the systemic inflammatory response has been demonstrated to have prognostic value in AP²⁷. This indicated the validity and practicality of the proposed ranking methods of the classification system.

The primary advantage of the classification system is simplicity. There were only three procedures to determine the type of a patient. There is no need for additional computation. In addition, the parameters in each step can be easily obtained early on in the course following hospital admission. The parameters involved in the classification system were all objective.

A strength of the current study was that the classification system was prospectively applied to the clinical practice to precisely direct clinical treatment. The complexity of ABP regarding its course, severity, prognosis, accompanying diseases in the biliary system, and the variety of available interventions have raised the need for multidisciplinary management and individualization of every case. However, there is a

paucity of data as to which treatment, including cholecystectomy, endoscopic retrograde cholangiopancreatography and sphincterotomy, and what time, which is optimal, especially in severe biliary pancreatitis²⁸. In this classification system, early laparoscopic cholecystectomy is recommended for patients with Type I; early biliary sphincterotomy and endoscopic duct clearance alone is suggested for Type II; for Type III, biliary sphincterotomy, endoscopic duct clearance, or choledochotomy is recommended. Furthermore, it is recommended that patients diagnosed with CBDS are offered stone extraction if possible. Early continuous regional arterial infusion was carried out in patients with Type III/IV. Although widespread consensus regarding the important role of cholecystectomy in the management of ABP, discrepancy between guideline recommendations for early cholecystectomy and actual rates of implementation has been reported, ranging from 32–67%^{28–32}. In a nationwide survey across England, the overall rate of early definitive treatment was only 34.7%¹⁸. The rate of early definitive treatment increased significantly with the addition of the guidance by current classification system in patients with Type I/II, from 35.9–77.4% ($P < 0.001$), by which recurrence rate and associated costs can potentially be reduced³³. In the current study, CRAI was recommended as an early definitive treatment for patients with Type III/IV, in which the mortality has clearly descended.

To the best of our knowledge, this was the first classification system for ABP. Physicians could assort an individual into a clinical type accurately through this easy-to-use classification system. Identifying each type of patients had an impact on the treatment or care option. Furthermore, this tool can provide information for the design of clinical studies, gaining better equivalence between study arms. Nevertheless, the data were collected at a single center. Further efforts to test the classification system in clinical application at a multicenter approach with wider geographic recruitment are encouraged.

In summary, we have developed a simple clinical classification system for use in ABP. With the guidance by the classification system, the rate of early definitive treatment in patients with ABP was improved and mortality was reduced. The classification system can strengthen decision making for each patient. Nevertheless, the classification system will have to stand the test of clinical application at a multicenter level.

Conclusions

In conclusion, for patients with acute biliary pancreatitis, we present a simple clinical classification system with 4 distinct types, with 2 subtypes for guiding the early-definitive treatment for acute biliary pancreatitis.

List Of Abbreviations

ABP, acute biliary pancreatitis; AP, acute pancreatitis; BISAP, bedside index for severity in acute pancreatitis; BUN, blood urea nitrogen; CBDS, common bile duct stones; CRAI, continuous regional arterial infusion; IQR, interquartile range; MODS, multiple organ dysfunction syndrome; SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome; WBC, white blood cell

Declarations

Ethics approval and consent to participate:

The research protocol of the study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (Ethics number: 2017-197). The study was registered in the Chinese Clinical Trial Registry (ChiCTR-OOC-17013097).

Consent for publication:

Not applicable

Availability of supporting data:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare no conflicting financial interests.

Funding:

This work was supported by grants from National Natural Sciences Foundation of China (81700568, 81570853, 81770630, 81800567 and 81900583), Zhejiang Medical And Health Science and Technology Plan Project (2018RC056) And Wenzhou Basic Scientific Research Projects(Y20180226 and Y20180103).

Authors' Contributions:

HW.S. and KQ.S. designed the study and supervised the study. SJ.D., HR.K., M.W., Z.C. and HJ.Y. collected and organized clinical information from Pancreatitis Unit of the First Affiliated Hospital of Wenzhou Medical University. KQ.S., YP.J. and YF.S. analyzed the clinical and experimental data.

Acknowledgements:

The data in current study was extracted by Lex Clinical Data Application 1.0 (Shanghai Lejiu Healthcare Technology Co., Ltd) from the Hospital Health Information System (HIS). The study was registered in Chinese Clinical Trial Registry (ChiCTR-OOC-17013097).

References

1. Lankisch PG, Apte M, Banks PA: Acute pancreatitis. Lancet 2015; 386: 85-96.
2. Szentesi A, Toth E, Balint E, Fanczal J, Madacsy T, Laczko D et al.: Analysis of research activity in gastroenterology: Pancreatitis is in real danger. PLoS One 2016; 11: e0165244.

3. Petrov MS, Yadav D: Global epidemiology and holistic prevention of pancreatitis. *Nat Rev Gastroenterol Hepatol* 2019; 16: 175-184.
4. Swaroop VS, Chari ST, Clain JE: Severe acute pancreatitis. *Jama* 2004; 291: 2865-2868.
5. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN, American Gastroenterological Association Institute Clinical Guidelines C: American gastroenterological association institute guideline on initial management of acute pancreatitis. *Gastroenterology* 2018; 154: 1096-1101.
6. Italian Association for the Study of the P, Pezzilli R, Zerbi A, Campra D, Capurso G, Golfieri R et al.: Consensus guidelines on severe acute pancreatitis. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2015; 47: 532-543.
7. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG et al.: Classification of acute pancreatitis–2012: Revision of the atlanta classification and definitions by international consensus. *Gut* 2013; 62: 102-111.
8. van Geenen EJ, van der Peet DL, Bhagirath P, Mulder CJ, Bruno MJ: Etiology and diagnosis of acute biliary pancreatitis. *Nat Rev Gastroenterol Hepatol* 2010; 7: 495-502.
9. Lammert F, Gurusamy K, Ko CW, Miquel JF, Mendez-Sanchez N, Portincasa P et al.: Gallstones. *Nat Rev Dis Primers* 2016; 2: 16024.
10. Williams E, Beckingham I, El Sayed G, Gurusamy K, Sturgess R, Webster G et al.: Updated guideline on the management of common bile duct stones (cbds). *Gut* 2017; 66: 765-782.
11. Williams EJ, Green J, Beckingham I, Parks R, Martin D, Lombard M et al.: Guidelines on the management of common bile duct stones (cbds). *Gut* 2008; 57: 1004-1021.
12. Working Group IAPAAPAG: Iap/apa evidence-based guidelines for the management of acute pancreatitis. *Pancreatology : official journal of the International Association of Pancreatology (IAP)* [et al] 2013; 13: e1-15.
13. Tenner S, Baillie J, DeWitt J, Vege SS, American College of G: American college of gastroenterology guideline: Management of acute pancreatitis. *The American journal of gastroenterology* 2013; 108: 1400-1415; 1416.
14. Working Party of the British Society of G, Association of Surgeons of Great B, Ireland, Pancreatic Society of Great B, Ireland, Association of Upper GISoGB et al.: Uk guidelines for the management of acute pancreatitis. *Gut* 2005; 54 Suppl 3: iii1-9.
15. Gurusamy KS, Belgaumkar AP, Haswell A, Pereira SP, Davidson BR: Interventions for necrotising pancreatitis. *Cochrane Database Syst Rev* 2016; 4: CD011383.
16. Dedemadi G, Nikolopoulos M, Kalaitzopoulos I, Sgourakis G: Management of patients after recovering from acute severe biliary pancreatitis. *World J Gastroenterol* 2016; 22: 7708-7717.
17. Tse F, Yuan Y: Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst Rev* 2012: CD009779.

18. Green R, Charman SC, Palser T: Early definitive treatment rate as a quality indicator of care in acute gallstone pancreatitis. *The British journal of surgery* 2017; 104: 1686-1694.
19. Mofidi R, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW: Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *The British journal of surgery* 2006; 93: 738-744.
20. Endo A, Shiraishi A, Fushimi K, Murata K, Otomo Y: Impact of continuous regional arterial infusion in the treatment of acute necrotizing pancreatitis: Analysis of a national administrative database. *J Gastroenterol* 2018.
21. Yong FJ, Mao XY, Deng LH, Zhang MM, Xia Q: Continuous regional arterial infusion for the treatment of severe acute pancreatitis: A meta-analysis. *Hepatobiliary Pancreat Dis Int* 2015; 14: 10-17.
22. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA: The early prediction of mortality in acute pancreatitis: A large population-based study. *Gut* 2008; 57: 1698-1703.
23. Hong W, Lin S, Zippi M, Geng W, Stock S, Basharat Z et al.: Serum albumin is independently associated with persistent organ failure in acute pancreatitis. *Can J Gastroenterol Hepatol* 2017; 2017: 5297143.
24. Peng T, Peng X, Huang M, Cui J, Zhang Y, Wu H et al.: Serum calcium as an indicator of persistent organ failure in acute pancreatitis. *Am J Emerg Med* 2017; 35: 978-982.
25. Yin G, Hu G, Cang X, Yu G, Hu Y, Xing M et al.: C-reactive protein: Rethinking its role in evaluating the severity of hyperlipidemic acute pancreatitis. *Pancreas* 2014; 43: 1323-1328.
26. Hong W, Dong L, Huang Q, Wu W, Wu J, Wang Y: Prediction of severe acute pancreatitis using classification and regression tree analysis. *Dig Dis Sci* 2011; 56: 3664-3671.
27. Jain S, Midha S, Mahapatra SJ, Gupta S, Sharma MK, Nayak B et al.: Interleukin-6 significantly improves predictive value of systemic inflammatory response syndrome for predicting severe acute pancreatitis. *Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al]* 2018.
28. van Baal MC, Besselink MG, Bakker OJ, van Santvoort HC, Schaapherder AF, Nieuwenhuijs VB et al.: Timing of cholecystectomy after mild biliary pancreatitis: A systematic review. *Ann Surg* 2012; 255: 860-866.
29. Nguyen GC, Rosenberg M, Chong RY, Chong CA: Early cholecystectomy and ercp are associated with reduced readmissions for acute biliary pancreatitis: A nationwide, population-based study. *Gastrointest Endosc* 2012; 75: 47-55.
30. Nguyen GC, Tuskey A, Jagannath SB: Racial disparities in cholecystectomy rates during hospitalizations for acute gallstone pancreatitis: A national survey. *The American journal of gastroenterology* 2008; 103: 2301-2307.
31. El-Dhuwaib Y, Deakin M, David GG, Durkin D, Corless DJ, Slavin JP: Definitive management of gallstone pancreatitis in england. *Ann R Coll Surg Engl* 2012; 94: 402-406.
32. Murphy PB, Paskar D, Parry NG, Racz J, Vogt KN, Symonette C et al.: Implementation of an acute care surgery service facilitates modern clinical practice guidelines for gallstone pancreatitis. *J Am Coll*

Surg 2015; 221: 975-981.

33. Ragnarsson T, Andersson R, Ansari D, Persson U, Andersson B: Acute biliary pancreatitis: Focus on recurrence rate and costs when current guidelines are not complied. Scand J Gastroenterol 2017; 52: 264-269.

Tables

Table 1.
Baseline characteristics of patients in retrospective and prospective cohort

Variable	Retrospective cohort (n = 2951)	Prospective cohort (n = 323)	P value
Clinical parameters			
Age, years (median, IQR)	54.1 (42.6, 67.0)	55.4 (42.5, 70.5)	0.141
Male gender (n, %)	1669 (56.6%)	177 (54.8%)	0.545
Laboratory parameters			
ALT, U/L (median, IQR)	53.0 (22.0, 161.5)	11.0 (7.0, 16.0)	0.001
AST, U/L (median, IQR)	45.0 (23.0, 109.0)	58.0 (28.0, 160.0)	0.001
Total bilirubin, $\mu\text{mol/L}$ (median, IQR)	20.0 (13.0, 39.0)	23.0 (13.5, 42.0)	0.388
DB/TB (median, IQR)	0.50 (0.32, 0.63)	0.50 (0.32, 0.59)	0.020
Albumin, g/L (median, IQR)	36.6 (32.8, 40.1)	36.5 (31.9, 40.4)	0.602
Triglyceride, mmol/L (median, IQR)	1.14 (0.75, 2.07)	1.05 (0.66, 2.04)	0.190
Creatinine, mg/dl (median, IQR)	65.0 (53.0, 79.0)	62.0 (50.0, 77.0)	0.273
Glucose, mg/dl (median, IQR)	7.80 (6.30, 10.0)	7.55 (6.20, 9.80)	0.138
WBC $10^9/\text{L}$ (median, IQR)	10.7 (7.6, 14.8)	11.9 (8.5, 16.0)	0.007
Serum Calcium, mmol/L (median, IQR)	2.18 (2.06, 2.28)	2.16 (2.01, 2.27)	0.060
Biliary obstruction (n, %)	799 (27.1%)	92 (28.5%)	0.589
Common bile duct stone (n, %)	888 (30.1%)	91 (28.2%)	0.475
SIRS (n, %)	666 (22.6%)	86 (26.6%)	0.100
Marshall score			
≥ 2	394 (13.4%)	97 (30.0%)	0.001
< 2	2793 (86.6%)	226 (70.0%)	
BISAP score (mean $\pm$ SD)	0.83 $\pm$ 0.85	1.17 $\pm$ 0.97	0.001
Classification system (n, %)			
Ia	277 (9.4%)	24 (7.4%)	
Ib	1599 (54.2%)	129 (39.9%)	
IIa	497 (16.8%)	47 (14.6%)	
IIb	184 (6.2%)	26 (8.0%)	

IIIa	70 (2.4%)	11 (3.4%)	
IIIb	48 (1.6%)	8 (2.5%)	
IVa	44 (1.5%)	7 (2.2%)	
IVb	232 (7.9%)	71 (22.0%)	
Hospital stays, days (median, IQR)	11 (8, 16)	15 (10, 21)	0.001
Mortality* (n,%)	69 (2.3%)	4 (1.2%)	0.317
<p>*: Sixty patients (15.2%) and 4 (4.1%) patients died in Type III/IV in retrospective cohort and prospective cohort, respectively (P = 0.001);</p> <p>ALT, alanine aminotranferase; ALP, alkaline phosphatase; AST, aspartate aminotranferase; BISAP, bedside index of severity in acute pancreatitis; GGT, gamma-glutamyl transferase; SIRS, systemic inflammatory response syndrome</p>			

Table 2.
Characteristics of patients according to the classification system in retrospective cohort

Variable	Classification system			
	Type I (n=1877)	Type II (n = 681)	Type III (n = 118)	Type IV (n = 276)
Age, years (median, IQR)	50.1 (40.4, 63.1)	61.2 (49.9, 72.6)	68.2 (59.7, 77.2)	58.0 (41.7, 73.5)
Male gender (n, %)	1074 (57.2%)	353 (51.8%)	66 (55.9%)	176 (63.8%)
SIRS present				
WBC 10 ⁹ /L (median, IQR)	10.5 (7.7, 14.5)	10.5 (7.7, 14.5)	13.1 (8.0, 17.3)	13.1 (8.0, 21.8)
Temperature, °C (median IQR)	37.0 (36.7, 37.5)	37.0 (36.7, 37.4)	37.3 (36.8, 37.8)	37.2 (36.8, 37.8)
Pulse, beats/min (median, IQR)	81 (72, 92)	80 (70, 88)	89.5 (76.5, 100)	90.0 (78.0, 104.0)
Respirations/min, (median, IQR)	20 (20, 20)	20 (20, 20)	20 (20, 20)	20 (20, 20)
Systolic blood pressure, mmHg (median, IQR)	127 (113, 142)	125 (113, 141)	130 (112, 144)	130 (112, 147)
Blood urea nitrogen, mg/dl (median, IQR)	4.65 (3.50, 6.00)	5.10 (3.80, 6.50)	7.00 (4.90, 11.20)	6.00 (4.30, 10.2)
Creatinine, mg/dl (median, IQR)	64.0 (53.0, 77.0)	63.0 (52.0, 77.0)	78.0 (61.8, 99.0)	72.0 (56.0, 96.0)
Glucose, mg/dl (median, IQR)	7.70 (6.30, 10.0)	7.75 (6.40, 9.50)	8.00 (6.07, 10.13)	8.20 (6.41, 11.13)
Triglyceride, mmol/L (median, IQR)	1.21 (0.78, 2.39)	0.94 (0.66, 1.46)	0.93 (0.69, 1.49)	1.40 (0.82, 3.33)
ALT, U/L (median, IQR)	40.0 (19.0, 125.8)	129.0 (44.0, 283.0)	96.0 (54.0, 220.8)	36.5 (17.0, 80.1)
AST, U/L (median, IQR)	34.0 (21.0, 81.0)	93.0 (37.0, 205.8)	82.0 (42.0, 184.0)	39.5 (24.0, 74.5)
Total bilirubin, µmol/L (median, IQR)	17.0 (12.0, 26.0)	39.0 (20.0, 79.5)	45.0 (24.0, 78.0)	18.0 (11.0, 27.3)
DB/TB (median, IQR)	0.57 (0.43, 0.64)	0.33 (0.22, 0.53)	0.32 (0.18, 0.50)	0.50 (0.36, 0.61)
Albumin, g/L (median, IQR)	37.4 (33.9, 40.5)	36.2 (32.6, 39.8)	33.2 (30.1, 36.5)	32.6 (28.8, 36.7)
Serum Calcium, mmol/L (median, IQR)	2.19 (2.08, 2.29)	2.20 (2.11, 2.29)	2.13 (1.94, 2.23)	2.05 (1.91, 2.21)

C reactive protein, mg/L (median, IQR)	28.2 (8.5, 90)	28.9 (9.4, 68.4)	75.9 (32.6, 90.0)	65.3 (17.5, 90.0)
Pleural effusion (n, %)	104/547 (19.0%)	16/158 (10.1%)	59/85 (69.4%)	149/188 (79.3%)
Common bile duct stone (n, %)	277 (14.8%)	497 (73.0%)	70 (59.3%)	44 (15.9%)
Hospital stays days,(median, IQR)	10 (7, 15)	12 (9, 17)	13 (8, 17.3)	12 (8, 21.8)
Mortality (n,%)	8 (0.4%)	1 (0.1%)	20 (16.9%)	40 (14.5%)
ALT, alanine aminotranferase; AST, aspartate aminotranferase; BISAP, bedside index of severity in acute pancreatitis; DB, direct bilirubin; TB, total bilirubin; IQR, interquartile range; SIRS, systemic inflammatory response syndrome				

Table 3.
Characteristics of patients according to the classification system in prospective cohort

Variable	Classification system			
	Type I (n=153)	Type II (n = 73)	Type III (n = 19)	Type IV (n = 78)
Age (median, IQR)	57.4 (45.1, 70.5)	60.8 (50.7, 73.8)	65.5 (51.2, 80.0)	44.8 (35.5, 57.1)
Male gender (n, %)	83 (54.2%)	34 (46.6%)	9 (47.4%)	51 (65.4%)
SIRS present				
WBC 10 ⁹ /L (median, IQR)	10.8 (7.3, 14.7)	11.9 (9.3, 15.9)	9.3 (7.0, 16.5)	13.9 (10.2, 18.1)
Temperature, °C (median IQR)	37.1 (36.8, 37.4)	37.2 (37.0, 37.4)	37.0 (37.0, 37.7)	37.5 (37.0, 37.9)
Pulse, beats/min (median, IQR)	80 (73, 89)	84 (72, 89)	84 (75, 92)	88 (80, 109)
Respirations/min, (median, IQR)	20 (20, 20)	20 (20, 20)	20 (20, 20)	20 (20, 20)
Systolic blood pressure, mmHg (median, IQR)	123 (113, 137)	116 (105, 133)	115 (100, 143)	120 (110, 133)
Blood urea nitrogen, mg/dl (median, IQR)	4.65 (3.32, 6.13)	5.50 (4.20, 7.40)	5.00 (4.20, 8.80)	5.20 (3.80, 6.85)
Creatinine, mg/dl (median, IQR)	63.0 (50.0, 76.0)	63.0 (49.5, 76.0)	65.0 (47.0, 90.0)	61.5 (49.0, 83.0)
Glucose, mg/dl (median, IQR)	7.15 (5.90, 9.58)	7.80 (6.57, 9.93)	7.10 (5.40, 9.20)	8.20 (6.20, 10.90)
Triglyceride, mmol/L (median, IQR)	1.00 (0.70, 1.46)	0.74 (0.47, 1.17)	0.82 (0.54, 5.56)	2.79 (1.08, 9.22)
ALT, U/L (median, IQR)	9.0 (7.0, 14.0)	13.0 (9.0, 17.5)	9.50 (5.00, 16.3)	10.0 (6.0, 15.0)
AST, U/L (median, IQR)	49.5 (24.0, 162.0)	125 (56.8, 233.3)	45.5 (23.8, 180.8)	41.0 (28.0, 101.0)
Total bilirubin, µmol/L (median, IQR)	19.0 (12.0, 32.0)	42.0 (25.0, 72.0)	18.0 (10.8, 55.3)	20.0 (12.8, 28.3)
DB/TB (median, IQR)	0.50 (0.39, 0.61)	0.33 (0.22, 0.52)	0.48 (0.31, 0.64)	0.50 (0.35, 0.59)
Albumin, g/L (median, IQR)	37.6 (34.3, 41.2)	36.3 (32.4, 39.4)	31.0 (28.2, 34.7)	33.6 (30.2, 40.4)
Serum Calcium, mmol/L (median, IQR)	2.21 (2.10, 2.30)	2.19 (2.10, 2.28)	2.07 (1.84, 2.17)	2.02 (1.85, 2.16)
C reactive protein, mg/L (median,	17.9 (5.1,	27.1 (8.4,	53.4 (17.7,	48.7 (14.2,

IQR)	58.8)	48.8)	90.0)	168.9)
Pleural effusion (n, %)	30 (19.6%)	19 (26.0%)	11 (57.9%)	43 (55.1%)
Common bile duct stone (n, %)	24 (15.7%)	47 (64.4%)	13 (68.4%)	7 (9.0%)
Hospital stays days,(median, IQR)	12.1 (8.9, 16.8)	13.6 (9.9, 18.2)	21.0 (14.8, 31.0)	21.3 (16.0, 29.4)
Mortality (n,%)	0	0	0	4 (5.1%)
ALT, alanine aminotranferase; AST, aspartate aminotranferase; BISAP, bedside index of severity in acute pancreatitis; DB, direct bilirubin; TB, total bilirubin; IQR, interquartile range; SIRS, systemic inflammatory response syndrome				

Table 4.
The early definitive treatments for Type I/II in prospective cohort

Treatments	Type I-a (n=24)	Type I-b (n=129)	Type II-a (n=47)	Type II-b (n=26)
Cholecystectomy	11	73	14	3
ERCP	9	7	22	16
Choledochotomy	2	0	2	0
ERCP+ cholecystectomy	2	1	8	1
ERCP, endoscopic retrograde cholangiopancreatography				

Table 5.
The early definitive treatments for Type I/II in prospective cohort.

Traetments	Type III-a (n = 11)	Type III-b (n = 8)	Type IV-a (n = 7)	Type IV-b (n = 7)
Continuous regional arterial infusion	1	7	4	67
ERCP	4	0	0	0
Choledochotomy	1	0	0	0
Continuous regional arterial infusion +ERCP	2	0	1	0
Continuous regional arterial infusion + Choledochotomy	2	0	0	0
ERCP+ Choledochotomy	1	0	1	0
ERCP, endoscopic retrograde cholangiopancreatography				

Figures

Figure 1

The flow chart of the classification system for acute biliary pancreatitis.

Figure 1

The flow chart of the classification system for acute biliary pancreatitis.

Figure 2

The schematic diagram of each type in the classification system.

Figure 2

The schematic diagram of each type in the classification system.

Figure 3

A flow diagram of study participants. AP, acute pancreatitis; ABP, acute biliary pancreatitis

Figure 3

A flow diagram of study participants. AP, acute pancreatitis; ABP, acute biliary pancreatitis

Figure 4

BISAP score in each type of acute biliary pancreatitis. (A) retrospective cohort; (B) prospective cohort. BISAP, bedside index for severity in acute pancreatitis

Figure 4

BISAP score in each type of acute biliary pancreatitis. (A) retrospective cohort; (B) prospective cohort. BISAP, bedside index for severity in acute pancreatitis

Figure 5

The present of SIRS and the proportion of two or more positive SIRS criteria in each type of acute biliary pancreatitis. (A) retrospective cohort; (B) prospective cohort. SIRS, systemic inflammatory response syndrome

Figure 5

The present of SIRS and the proportion of two or more positive SIRS criteria in each type of acute biliary pancreatitis. (A) retrospective cohort; (B) prospective cohort. SIRS, systemic inflammatory response syndrome

Figure 6

The rate of early definitive treatment in patients with Type I/II in retrospective cohort and prospective cohort.

Figure 6

The rate of early definitive treatment in patients with Type I/II in retrospective cohort and prospective cohort.

Figure 7

The mortality in patients with Type III/IV in retrospective cohort and prospective cohort.

Figure 7

The mortality in patients with Type III/IV in retrospective cohort and prospective cohort.