Comparison of differences between initial and recurrent acute pancreatitis in the intensive care unit

Abstract

Introduction

Previous studies have found that RAP may be at reduced risk for a clinically severe course and have reduced mortality. However, there is still a lack of data related to RAP admitted to ICU.

Material and methods

Baseline characteristics of patients diagnosed with IAP and RAP from the MIMIC-IV database were extracted. In-hospital mortality and length of hospital/ICU stay were identified as outcomes. Binomial logistic regression analysis was performed to clarify the independent risk factors for in-hospital mortality in both groups, and we determined the best scoring system for prognosis prediction by plotting the ROC curves and DCA curves.

Results

The in-hospital mortality rate was 13.96% in patients with IAP and 3.57% in patients with RAP. For IAP, the CCI, the BISAP score, and the SIRS score on the first day of admission were independent risk factors for in-hospital mortality. The SAPS II score almost always showed a higher net clinical benefit than the other scoring systems (BISAP, LODS, and OASIS). The BISAP score almost always showed a higher net clinical benefit than the others for RAP.

Conclusions

RAP is less severe and has a lower risk of in-hospital mortality than IAP. The CCI, the BISAP score, and the SIRS score on the first day of admission were all independent risk factors for in-hospital mortality in patients with IAP. The SAPS II score was a better scoring system for predicting in-hospital mortality in patients with IAP. The BISAP score showed potential for predicting in-hospital mortality in patients with RAP.

Comparison of differences between initial and recurrent acute pancreatitis in the intensive care unit

Running title: Differences Initial and Recurrent AP

1 **Abstract**

2 ***Background:*** Previous studies have found that patients with recurrent acute

3 pancreatitis (RAP) may be at reduced risk for a clinically severe course and have

4 reduced mortality. However, there is still a lack of data related to recurrent acute

5 pancreatitis admitted to intensive care unit (ICU).

6 ***Methods:*** Baseline characteristics of patients diagnosed with initial and recurrent

7 acute pancreatitis from the Medical Information Mart for Intensive Care/MIMIC-IV

8 database were extracted. In-hospital mortality and length of hospital/ICU stay were

9 identified as outcomes. Binomial logistic regression analysis was performed to clarify

10 the independent risk factors for in-hospital mortality in both groups, and we

11 determined the best scoring system for prognosis prediction by plotting the receiver

12 operating characteristic (ROC) curves and the decision curve analysis (DCA) curves.

13 ***Results:*** The in-hospital mortality rate was 13.96% in patients with initial acute

14 pancreatitis (IAP) and 3.57% in patients with RAP, and there was no statistical

15 difference between the two groups regarding length of hospital/ICU stay. For IAP, the

16 Charlson comorbidity index, the Bedside Index for Severity in Acute Pancreatitis

17 (BISAP) score, and the Systemic Inflammatory Response Syndrome (SIRS) score on

18   the first day of admission were independent risk factors for in-hospital mortality. Age,

19   gender, Charlson comorbidity index, BISAP score, SIRS score, and obesity were not

20   independent risk factors for in-hospital mortality in patients with RAP. For patients

21   with IAP, the areas under the ROC curves (AUCs) of the four scoring systems [the

22   BISAP, the Logistic Organ Dysfunction System (LODS), the Oxford Acute Severity

23   of Illness Score (OASIS), and the Simplified Acute Physiology Score II (SAPS II)]

24   were 0.720, 0.847, 0.808, and 0.845, respectively, but the results of the Z test showed

25   no statistical difference between LODS and SAPS II; The DCA showed that in the

26   threshold of 0.2-0.6, SAPS II score almost always showed a higher net clinical benefit

27   than the other scoring systems, while the threshold exceeded 0.6, none of the four

28   scoring systems showed a net clinical benefit. For patients with RAP, the AUCs of the

29   four scoring systems (BISAP, LODS, OASIS, and SAPS II) were 0.944, 0.861, 0.681,

30   and 0.829, respectively, but the AUC value of BISAP was only statistically different

31   from that of LODS; The DCA showed that in the threshold of 0 -0.25, BISAP score

32   almost always showed a higher net clinical benefit than the other scoring systems, but

33   in other threshold ranges, none of the four scoring systems showed a net clinical

34   benefit.

35   *Conclusions:* RAP is less severe and has a lower risk of in-hospital mortality than IAP.

36   The Charlson comorbidity index, the BISAP, and the SIRS score on the first day of

37   admission were all independent risk factors for in-hospital mortality in patients with

38   IAP. The SAPS II score was a better scoring system for predicting in-hospital

39   mortality in patients with IAP. In contrast, the BISAP score showed potential for

40   predicting in-hospital mortality in patients with RAP.

41

44

1.   Introduction

46   Acute pancreatitis (AP) is one of the most common and critical diseases of the

47   digestive system. It has been reported that 5-35 people per 100,000 seek medical

48   attention for AP each year, and the incidence has been on the rise for the past two

49   decades[1, 2]. Approximately 15-20% of patients with AP develop moderate or severe

50   disease. At this level of severity, patients may develop multi-organ failure with a

51   mortality rate of 20-40%, and these patients often require admission to an intensive

52   care unit (ICU)[3]. Meanwhile, AP is exceptionally prone to recurrence when the

53   underlying cause of its onset is not found or when the underlying cause is not

54   eliminated, and its recurrence rate is between 10% and 30%[4, 5]. Recurrent acute

55   pancreatitis (RAP) affects patients' quality of life and increases the burden of

56   healthcare costs for patients[6]. In addition, RAP is also a significant risk factor for

57   progression to chronic pancreatitis[7]. Other studies have suggested that RAP may be

58   associated with pancreatic cancer[8].

59   A study by Lee et al. [4]retrospectively analyzed the clinical outcomes of 292

60   patients with AP (213 patients with IAP and 79 patients with RAP) who attended the

61   Cleveland Clinic between 2008 and 2011 and found a mortality rate of 4.7% for IAP

62   patients and 0% for patients with RAP (p = 0.047). The investigators concluded that

63   patients with RAP may be at reduced risk of a clinically severe course and have

64   reduced mortality. In addition, after adjusting for potential confounders (e.g., transfer

65   status, obesity), they found that prior episodes of AP were protective against

66   multisystem organ failure and admission to the ICU in RAP. However, few studies

67   have compared the differences between RAP and IAP, and there is a lack of data

68   related to RAP admission to the ICU. This study is intended to further elucidate the

69   differences between IAP and RAP based on a large public database (the Medical

70   Information Mart for Intensive Care, MIMIC-IV), to provide clinical evidence on

71   allocating healthcare resources related to AP.

72

73   **2.   Methods**

74   *2.1 Introduction to the database*

75   The MIMIC is a database of intensive care medicine, established in 2003 with

76   funding from the National Institutes of Health (NIH) by emergency physicians,

77   intensivists, and computer science experts from Beth Israel Deaconess Medical Center,

78   Massachusetts Institute of Technology, Oxford University, and Massachusetts General

79   Hospital[9], and has been updated to version 4 (MIMIC-IV, https://mimic.mit.edu/).

80   The MIMIC-IV database currently collects information on more than 70,000 critical

81   care hospitalizations, which is far more cases than any single-center clinical trial site

82   worldwide. The data collection and entry process of the MIMIC-IV is done by

83   professionally trained personnel and can be considered a high-quality multi-center

84   clinical research database.

2.2 Study population

86   Patients with AP were identified according to the ICD codes of the diagnosis and

87   those admitted to the hospital or ICU for chronic pancreatitis were excluded from this

88   study. The following information was extracted for included patients using Navicat

89   software (version 16.1.3): age, gender, race (white, black, and other ethnicities),

90   Charlson comorbidity index, presence of acute kidney injury/sepsis/obesity, BISAP

91   (Bedside Index for Severity in Acute Pancreatitis) score, SIRS (Systemic

92   Inflammatory Response Syndrome) score, LODS (Logistic Organ Dysfunction

93   System) score[10], OASIS (Oxford Acute Severity of Illness Score) score[11], SAPS

94   II (Simplified Acute Physiology Score Ⅱ) score[12], laboratory tests (hemoglobin,

95   red blood cells, red blood cell distribution width, platelets, white blood cells, anion

96   gap, blood urea nitrogen, creatinine, international normalized ratio, prothrombin time,

97   alanine aminotransferase, aspartate aminotransferase, total bilirubin, and blood

98   glucose), vital signs (heart rate, mean arterial pressure, respiratory rate, and body

99   temperature), fluid intake and urine output on the first day of admission. The BISAP

100   score[13] was introduced in 2008 and is cumulative with the presence of the

101   following: blood urea nitrogen >25 mg/dl, impaired mental status (Glasgow Coma

102   Score <15), SIRS, age >60 years, and presence of pleural effusion. BISAP score has

103   been shown to be useful for the early identification of AP with an increased risk of

104   in-hospital death patients[14-16]. However, the relationship between BISAP score and

105   prognosis of severe AP lacks large-scale data support.

106   RAP was defined as acute pancreatitis that occurred at least 2 months after the

107   last episode[4, 17, 18]. The time difference between the patient's admissions was

108   calculated using Python software (version 3.9), and the diagnosis of RAP was rejected

109   if the time difference between the two hospitalizations was less than 2 months.

110   *2.3 Statistical analysis*

111   Statistical analyses were performed using R software (version 4.1.2) and

112   Medcalc software (version 20.1.0). Patients with IAP and RAP were grouped, and

113   their basic characteristics were described. Continuous variables were first clarified

114   whether they obeyed normal distribution using the Kolmogorov-Smirnov test. If they

115   obeyed normal distribution (presented as mean ± standard deviation), the student t-test

116   was performed for comparison between groups, and if they did not obey normal

117   distribution (presented as a median and interquartile range), a non-parametric test

118   (Mann- Whitney U test) was performed for comparison between groups; Categorical

119   variables (presented as sample size and percentages) were compared between groups

120   using the chi-square test. Kaplan-Meier curves were plotted to clarify whether there

121   was a difference in survival between the two groups by the Log-rank test and

122   Tarone-Ware test. Binomial logistic regression analysis was performed to clarify the

123   independent risk factors for in-hospital mortality of the patients, where variables with

124   p-values <0.1 in the univariable regression analysis were included in the multivariable

125   regression analysis. The predictive value of the four scoring systems (LODS, OASIS,

126   and SAPS II have all been used for prognostic prediction in patients admitted to the

127   ICUs) for in-hospital mortality of the patients was further compared by plotting the

128 receiver operating characteristic (ROC) curves of each scoring system, and the area

129 under the curves (AUCs) were tested for differences by the method of Delong et al.

130 The decision curve analysis (DCA) was also performed to clarify the net clinical

131 benefit of each scoring system when applied to AP patients. p values less than 0.05

132 were considered statistically different.

133

134 **3.   Results**

135 *3.1 Epidemiological features of RAP*

136   We identified 6195 patient admissions with a diagnosis of AP from over 200,000

137 admissions in the MIMIC-IV database between 2008 and 2019. After excluding repeat

138 hospitalizations, a total of 4060 patients were diagnosed with AP, 541 of whom were

139 readmitted for RAP, and the time interval between the second episode of AP and the

140 initial episode was 154 (90-443) days. There were 151 in-hospital deaths (in-hospital

141 mortality rate of 4.29%) in patients with IAP and 4 in-hospital deaths (in-hospital

142 mortality rate of 0.74%) in patients with RAP, with a statistically significant

143 difference (p < 0.001) and an overall in-hospital mortality rate of 3.82%. There were

144 1344 admissions to the ICU (over 70,000 ICU admissions in the database) with AP,

145 and after excluding repeat admissions, there were 1030 independent individual

146 patients with the specific diagnoses shown in Table 1. Of these 1030 ICU admissions,

147 974 patients were diagnosed with IAP, of which 79 were diagnosed with biliary AP,

148 63 with alcohol induced AP, 6 with drug induced AP, and 5 with idiopathic AP; the

149 other 56 patients were diagnosed with RAP, of which 5 were diagnosed with alcohol

150   induced AP, 1 with biliary AP, and 1 with drug induced AP, and 5 with idiopathic AP,

151   while the etiology of the remaining 49 patients was unknown.

3.2 Baseline characteristics of the included patients

153   Patients with RAP were younger, had a lower Charlson comorbidity index, lower

154   BISAP and SIRS scores, and lower hemoglobin, blood urea nitrogen, creatinine,

155   alanine aminotransferase, aspartate aminotransferase, and total bilirubin levels than

156   those with IAP. The remaining baseline characteristics were not statistically different

157   between the two groups (Table 2).

3.3 Outcomes of the included patients

159   Among the included patients admitted to the ICU, the in-hospital mortality rate

160   was 13.96% (of the 974 patients, 136 died) for patients with IAP and 3.57% (of the 56

161   patients, 2 died) for RAP. The risk of in-hospital death was lower for RAP (RR=0.892,

162   95% CI=0.843-0.944), and the difference was statistically significant (p=0.025).

163   Patients in the IAP group were hospitalized for 10.7 days (5.8 -20.0 days) and stayed

164   in the ICU for 2.6 days (1.2 -6.0 days); patients in the RAP group were hospitalized

165   for 8.8 days (5.8 -18.3 days) and stayed in the ICU for 2.3 days (1.3 -4.5 days). There

166   was no statistical difference between the two groups regarding length of hospital stay

167   and length of stay in the ICU (Table 3).

3.4 Survival analysis and independent risk factors for in-hospital mortality

169   Kaplan-Meier curves were plotted for the survival of the two groups (Figure 1).

170   p=0.064 for the Log-rank test and p=0.048 for the Tarone-Ware test. Since the Log

171 rank test is more sensitive to differences in distant outcome events, the difference in

172 survival between the two groups is considered statistically significant here. The

173 median survival time was 66.9 days (60.8-133.2 days) for patients with IAP and could

174 not be calculated for patients with RAP (due to too few deaths), whose mean survival

175 time was 66.214 days (standard deviation of 6.874 days).

176   The results of the binomial logistic regression analysis showed that for IAP, the

177 Charlson comorbidity index and the BISAP/SIRS score on the first day may be

178 independent risk factors for in-hospital mortality (Table 4). Here, we tested for

179 covariance between age, BISAP, and SIRS using a linear regression equation with

180 variance inflation factor (VIF) values of 1.544, 1.648, and 1.155, respectively,

181 confirming the absence of covariance. However, age, sex, Charlson comorbidity index,

182 BISAP / SIRS score on the first day, and the presence of obesity were not independent

183 risk factors for in-hospital mortality in patients with RAP (Table 5). We also observed

184 that RAP was not an independent risk factor for in-hospital mortality relative to IAP

185 after adjusting for a range of confounders (Table 6).

186 *3.5 Scoring system selection for predicting in-hospital mortality*

187   For patients with IAP, the ROC results of the four scoring systems are shown in

188 Figure 2. The AUC values, optimal cutoff values, sensitivity, specificity, and Youden

189 index of the four scoring systems are presented in Table 7, with the following Z-test

190 results: BISAP vs. LODS with a Z value of 5.950, p<0.0001; BISAP vs. OASIS with

191 a Z-value of 3.785, p=0.0002; BISAP vs. SAPS II with a Z value of 5.838, p<0.0001;

192 LODS vs. OASIS with a Z-value of 2.647, p=0.0081; LODS vs. SAPS II with a Z

193   value of 0.183, p=0.8545; OASIS vs. SAPS II with a Z value of 2.710, p=0.0067. In

194   the DCA curves (Figure 3), the net clinical benefit of SAPS II was almost always

195   higher than that of the other scoring systems in the threshold range of 0.2-0.6.

196   However, none of the four scoring systems showed a net clinical benefit after the

197   threshold range 0.6.

198   For patients with RAP, the ROC results of the four scoring systems are shown in

199   Figure 4 and Table 8, with Z-test results of BISAP vs. LODS with a Z value of 2.427,

200   p=0.0152; BISAP vs. OASIS with a Z value of 1.418, p=0.1562; BISAP vs. SAPS II

201   with a Z-value of 0.843, p=0.3991; LODS vs. OASIS with a Z value of 0.976,

202   p=0.3288; LODS vs. SAPS II with a Z-value of 0.234, p=0.8149. OASIS vs. SAPS II,

203   Z-value 2.497, p=0.0125. In the DCA curves (Figure 5), the net clinical benefit of

204   BISAP was almost always higher than that of the other scoring systems in the

205   threshold range of 0 -0.25. However, none of the four scoring systems showed a net

206   clinical benefit in the other threshold ranges.

207

208   **4.**   **Discussion**

209   This study first investigated the prognostic differences in patients with AP in the

210   ICU, and our results were similar to those of Lee et al.[4] that patients with RAP had

211   lower severity (lower BISAP and SIRS scores on the first day of admission) and a

212   lower risk of in-hospital death than those with IAP. In addition, consistent with

213   previous studies, patients with RAP were younger and had a lower Charlson

214   comorbidity index. The Charlson comorbidity index[19] can be used to assess the

215 impact of co-morbidities other than the underlying disease that is currently the

216 primary treatment for the future survival of patients. It seems that we could attribute

217 the lower mortality in patients with RAP to lower age and Charlson comorbidity index.

218 However, the results of binomial logistic regression analysis suggest that age and

219 Charlson comorbidity index are not independent risk factors for in-hospital mortality

220 in patients with RAP, and only Charlson comorbidity index is independently

221 associated with in-hospital mortality in patients with IAP. The answer to the question

222 of why patients with RAP are more likely to be younger and have a lower comorbidity

223 index is not yet available from previous studies. It needs to be further explored at a

224 later stage. In addition to blood urea nitrogen, we also found that patients with RAP

225 had lower creatinine levels, alanine aminotransferase levels, aspartate

226 aminotransferase levels, and total bilirubin levels, which to some extent reflect the

227 liver and kidney function of the patients, suggesting that better liver and kidney

228 function in patients with RAP may also contribute to the low mortality rate. However,

229 from the causal inference perspective, we cannot yet explain why patients with RAP

230 have better hepatic and renal function.

231 Understanding the differences between IAP and RAP at the pathogenesis level

232 can help provide better treatment options for patients. The reason for the lower

233 severity of disease in patients with RAP may stem from the loss of alveolar cells and

234 pancreatic fibrosis due to each episode of pancreatitis. As a direct result of reduced

235 alveolar cells, there may be less pancreatic auto-digestion, necrosis, and a subsequent

236 less inflammatory cascade response[20]. In contrast, pancreatic fibrosis has been

237 shown to directly reduce the severity of patients with acute-on-chronic

238 pancreatitis[21]. Other researchers suggest that the protective immune mechanism of

239 the body is not activated during the IAP, and this protective immune mechanism may

240 protect the body in RAP[4]. However, starting from the three possible mechanisms

241 mentioned above, only enhancing protective immune mechanisms is a potential

242 therapy. With the flourishing development of molecular biology technologies,

243 including genomics, proteomics, and transcriptomics in recent years, there is reason to

244 believe that the essential differences between IAP and RAP (e.g., details on

245 differentially expressed genes, protein expression levels, and key transcription factors

246 in the development of the disease course in both types of AP) will be further

247 elucidated, thus providing robust evidence for precision medicine in AP.

248   For prognostic prediction of patients with AP admitted to the ICU, Huang et al.

249 developed a nomogram that showed good predictive performance[22]. We

250 investigated the predictive value of four preexisting scoring systems in the prognosis

251 of patients with AP, in which LODS, OASIS, and SAPS II were all used as prognostic

252 predictive scoring systems in the ICU and also showed good predictive value[23]. For

253 patients with IAP, SAPS II appears to be the superior predictive scoring system, and

254 although it has the highest AUC (0.847) and the highest Yonden index (0.5825), it is

255 equivalent in value to LODS in the Z test. However, the DCA curve suggests that the

256 net clinical benefit for patients may be higher when using the SAPS II score as a

257 predictive scoring system. DCA curves have been used extensively to evaluate the

258 clinical utility of a model, i.e., whether the model is worthy of being practiced

259 clinically[24-27]. The value of each DCA curve can be described using the net benefit

260 ratio, the magnitude of which is similar to the AUC of the ROC curve, i.e., the larger

261 the area under the DCA curve, the larger the net benefit ratio. As seen from Figure 3,

262 if we choose the threshold probability range of 0.2-0.6 corresponding to the horizontal

263 coordinate, SAPS II leads almost with any other three scoring systems. In the range

264 greater than 0.6, all scoring systems have no significant net benefit. However, for RAP,

265 the results were quite different, and BISAP appeared to show some advantage in

266 predicting the prognosis of RAP. The AUC value (0.944) and the Yonden index

267 (0.8889) were the highest when using the BISAP score for prognosis prediction of

268 RAP. However, compared to the other three scoring systems, there was only a

269 statistical difference with the AUC of LODS. Afterward, the DCA curve results

270 showed that the net benefit of BISAP was most significant between the threshold

271 probabilities 0- 0.25. In conclusion, the prognostic prediction should not be

272 generalized for patients with AP admitted to the ICU. In the case of patients with IAP,

273 selecting a critical care scoring system for prognostic prediction may be a better

274 choice, while in patients with RAP, the BISAP score may have some advantages.

275 Approximately 14-20% of patients with AP are reported to require intensive care due

276 to multi-organ dysfunction and/or failure, and multidisciplinary teamwork in intensive

277 care can reduce mortality from 30% to 10% in severe AP[28]. It is valuable to clarify

278 the clinical features of AP in intensive care, and considering that patients with

279 first-episode AP may be more severely ill, we believe that the importance of intensive

280 care in the management of patients with first-episode AP should be emphasized to

prevent the deterioration of the patient's condition in advance. In fact, there is no sufficiently reliable prognostic score to predict the occurrence of severe AP. The Guidelines for the Management of Patients with Severe Acute Pancreatitis, 2021 states that the BISAP score is likely the most appropriate predictor of the development of severe AP[29]. We demonstrated the potential of the BISAP score in the prognosis prediction of RAP, further enriching the clinical application value of BISAP. However, only some previous studies related to intensive care in RAP have been reported, and our study also fills this gap to some extent.

Even though both this study and the study by Lee et al.[4] suggest that patients with RAP may have a milder disease than the initial attack, but their relatively high mortality rate is still unacceptable to us. Determining the etiology of an acute pancreatitis attack is a key factor in preventing recurrence. Among the 56 patients with RAP included in this study, as we have previously stated, 5 cases were definite alcoholic AP (about 9%), while 1 case each of drug-induced AP and biliary AP, and the etiology of the remaining patients was unclear. It has been shown that after the first episode of alcoholic AP, 46% of patients experience at least one recurrence during 10-20 years of follow-up, along with an increased risk of developing chronic pancreatitis[30, 31]. In addition, personal alcohol consumption is not associated with RAP, nor is the type of alcoholic beverage associated with RAP[31]. However, there is definite evidence that smoking and obesity are risk factors for alcohol-induced RAP[32, 33]. Therefore, in patients with alcoholic AP, weight control and smoking cessation may be effective measures to prevent a recurrence. For biliary AP, removing

the gallbladder is necessary to prevent recurrence[34]. As for drug-induced AP,

discontinuation of potentially pathogenic drugs and follow-up may be helpful for

patients. Some drugs have also been used for the prevention of RAP, including

octreotide, pancreatic enzymes, and ursodeoxycholic acid[34], but there is a lack of

high-quality, evidence-based medical evidence. However, most opinions believe that

the etiology of idiopathic AP is biliary microstones or sphincter of Oddi dysfunction

that cannot be detected by conventional methods[34], and laparoscopic

cholecystectomy and necessary genetic testing may help to reduce recurrence[35]. In

addition to the causes mentioned above, anatomical variants of the pancreas and

genetic mutations are also possible causes of the development of AP[36]. Another

study has shown that AP is prone to recurrence even during treatment, and factors

such as uncontrolled systemic inflammatory response may be responsible for

recurrence in such patients[6]. It must be emphasized that AP recurrence is likely to

result from a combination of factors[6] and any cause of AP that is not adequately

corrected may lead to recurrent attacks. In a word, to reduce the occurrence of RAP,

primary, secondary, and tertiary preventive measures should be systematically

implemented to mitigate the effects of AP and its sequelae as soon as possible.

Personal education of patients, effective in-hospital management, and screening of

high-risk patients all contribute to the prevention of RAP[37].

All in all, the strength of this study is that the study population was derived from

a large clinical database, presenting the clinical characteristics of RAP in intensive

care and the independent risk factors affecting their mortality in the largest possible

325 sample size, as well as comparing the scoring systems related to the prediction of their

326 mortality and comparing them more comprehensively with the characteristics of

327 patients with IAP during the same period. This fills the gap that the current study

328 population for RAP originates only from general gastroenterology and is instructive

329 for the management of AP patients in the ICU. Moreover, we report for the first time

330 that there was no significant difference between patients with IAP and patients with

331 RAP in terms of length of hospitalization and length of stay in the ICU as secondary

332 outcomes. Meanwhile, we confirmed that for the prognostic prediction of RAP

333 patients, the BISAP score possesses a greater advantage, and can achieve a greater net

334 clinical benefit for patients while ensuring predictive efficacy. Therefore, the BISAP

335 scoring system may be the preferred option for prognostic prediction of RAP patients

336 in future clinical practice. However, we must acknowledge certain limitations of this

337 study. Firstly, we did not explore the relationship between the number of episodes and

338 the prognosis of AP, due to the extensive time span of this database and the lack of

339 uniformity in follow-up, which makes it difficult to normalize the number of episodes;

340 secondly, this study is based on the US population and it remains unknown whether

341 all the conclusions obtained are applicable to populations in other countries or regions;

342 further, due to the large number of missing values in the database for amylase, lipids

343 (some studies have shown that elevated LDL cholesterol levels is an independent risk

344 factor for RAP[5]) and other laboratory tests, and we were unable to obtain imaging

345 data (including whether the pancreas was necrotic, formed pseudocysts or abscesses,

346 etc.) of the patients, the impact of these indicators on the outcomes was not explored,

347 which may affect the stability of the results; meanwhile, we were unable to grade the

348 patients in terms of severity based on methods such as the Atlanta Classification.

349 Unfortunately, as shown in Table 1, the etiology of most patients was also unknown to

350 us. Lastly, considering the small number of patient cases in the RAP group, the

351 stability of the results remains to be tested. Therefore, a rigorously designed

352 prospective randomized controlled clinical trial with a large sample is still essential to

353 thoroughly elucidate the differences between IAP and RAP.

354

5. Conclusion

356 RAP was less severe and had a lower risk of in-hospital mortality than IAP. For

357 IAP, the Charlson comorbidity index and the BISAP / SIRS score on the first day of

358 admission were independent risk factors for in-hospital death; no independent risk

359 factors for in-hospital death in patients with RAP were identified in this study. The

360 SAPS II score is a better scoring system for predicting in-hospital mortality in patients

361 with IAP. In contrast, the BISAP score showed some potential in predicting

362 in-hospital mortality in patients with RAP.

363

Disclosure statement

368 The authors have no competing interests to declare.

CRediT authorship contribution statement

All authors have read and agreed to the published version of the manuscript.

Ethics statement

Funding

Data availability

Data in the article can be obtained from MIMIC-IV database (version 0.4) (https://mimic.physionet.org/). The code for the data extraction is available on GitHub (https://github.com/MIT-LCP/mimic-iv).

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481

Table 1 Diagnosis of the included patients

Diagnosis	9th or 10th ICD code	No. of patients (Before/after elimination of duplicates)
Acute pancreatitis	5770，K859，K8590，K8591，K8592	1105/847
Biliary acute pancreatitis	K851，K8510，K8511，K8512	100/80
Alcohol induced acute pancreatitis	K852，K8520，K8521，K8522	93/68
Drug induced acute pancreatitis	K853，K8530，K8531	8/7
Idiopathic acute pancreatitis	K8500，K8502	10/5
Other acute pancreatitis	K858，K8580，K8581，K8582	28/23

483

484

Table 2 Baseline characteristics of the patients

Characteristics	IAP (n=974)	RAP (n=56)	p
Age, year	60.1 (47.6-73.5)	54.4 (40.6-68.2)	0.005
Gender (Male)	560 (57.49)	36 (64.29)	0.317
Ethnicity			0.055
White	617 (63.35)	35 (62.50)	
Black	100 (10.27)	11 (19.64)	
Others	257 (26.38)	10 (17.86)	
CCI	4 (3-7)	4 (2-6)	0.014
AKI	589 (60.47)	29 (51.79)	0.197
Sepsis	591 (60.68)	28 (50.00)	0.113
Obesity	119 (12.22)	6 (10.71)	0.738
Day 1 BISAP	2 (2-3)	2 (1-3)	0.024
Day 1 SIRS	3 (2-4)	3 (2-3)	0.003
Laboratory tests			
Hemoglobin,g/dL	10.9 (9.4-12.5)	10.3 (8.4-11.9)	0.019
RBC, 10^{12}/L	3.7 (3.1-4.1)	3.5 (2.9-3.8)	0.174
RDW, %	14.8 (13.8-17.1)	15.3 (14.0-16.9)	0.155
Platelets, 10^9/L	189 (131-265)	186 (126-308)	0.104
WBC, 10^9/L	12.5 (8.5-17.6)	9.5 (6.5-15.5)	0.089
Anion gap, mmol/L	15.5 (13.0-19.0)	15.3 (12.5-16.8)	0.296
BUN, mmol/L	20.3 (12.5-37.0)	17.3 (10.5-28.8)	0.042
Creatinine, mg/dL	1.1 (0.8-1.9)	0.9 (0.6-1.3)	0.024
INR	1.3 (1.2-1.6)	1.3 (1.1-1.5)	0.994
PT, s	14.3 (12.8-17.1)	13.8 (12.6-16.3)	0.846
ALT, U/L	51 (25-157)	31 (16-73)	0.003
AST, U/L	76 (36-182)	39 (19-134)	<0.001
TBil，μmol/L	1.1 (0.6-2.8)	0.6 (0.3-1.4)	<0.001
Glucose, mg/dL	131 (105-169)	131 (107-166)	0.722
Vital signs			
Heart rate, bpm	94 (81-107)	100 (86-109)	0.052
MAP, mmHg	80 (72-91)	82 (73-88)	0.488

RR, cpm	20 (17-24)	20 (17-24)	0.127
Temperature, ℃	37.0 (36.7-37.3)	36.9 (36.8-37.2)	0.902
Day 1 input, ml/day	10240 (5995-16420)	9681 (6445-14150)	0.636
Day 1 UO, ml/day	1484 (832-2349)	1920 (1228-2324)	0.140

485 IAP=Initial Acute Pancreatitis, RAP=Recurrent Acute Pancreatitis, CCI=Charlson Comorbidity
486 Index, AKI=Acute Kidney Injury, BISAP=Bedside Index for Severity in Acute Pancreatitis
487 Sequential, SIRS= Systemic Inflammatory Response Syndrome, RBC=Red Blood Cell, RDW=
488 Red cell Distribution Width, WBC=White Blood Cell, BUN=Blood Urea Nitrogen,
489 INR=International Normalized Ratio, PT=Prothrombin Time, ALT= Alanine aminotransferase,
490 AST=Aspartate aminotransferase, TBil=Total Bilirubin, MAP=Mean Artery Pressure, UO=Urine
491 Output.

492

493 **Table 3 Outcomes of the patients**

Outcomes	IAP (n=974)	RAP (n=56)	Relative Risk* (95% CI)	*p*
Death in hospital	136 (13.96)	2 (3.57)	0.892 (0.843-0.944)	0.025
LOS hospital (day)	10.7 (5.8-20.0)	8.8 (5.8-18.3)	/	0.507
LOS ICU (day)	2.6 (1.2-6.0)	2.3 (1.3-4.5)	/	0.497

494 CI=Confidence Interval, LOS= Length of Stay, ICU= Intensive Care Unit.
495 *Shown is the relative risk for recurrent acute pancreatitis versus initial acute pancreatitis.

496

497 **Table 4 Binomial Logistic regression analysis for in-hospital mortality among patients with**
498 **initial acute pancreatitis**

	Univariable		Multivariable	
	OR（95% CI）	*p*	OR（95% CI）	*p*
Age	1.034(1.022-1.046)	<0.001	1.000(0.984-1.016)	0.969
Gender (Male)	0.835(0.580-1.202)	0.332		
CCI	1.264(1.190-1.343)	<0.001	1.211(1.123-1.306)	<0.001
Day 1 BISAP	2.424(1.958-3.003)	<0.001	1.784(1.359-2.341)	<0.001
Day 1 SIRS	1.667(1.329-2.090)	<0.001	1.727(1.332-2.239)	<0.001
Obesity	0.875(0.493-1.554)	0.648		

499 OR=Odds Ratio, CI=Confidence Interval, CCI=Charlson Comorbidity Index, BISAP=Bedside
500 Index for Severity in Acute Pancreatitis Sequential, SIRS= Systemic Inflammatory Response
501 Syndrome.

502

503 **Table 5 Binomial Logistic regression analysis for in-hospital mortality among patients with**
504 **recurrent acute pancreatitis**

	Univariable		Multivariable	
	OR（95% CI）	*p*	OR（95% CI）	*p*
Age	1.106(0.978-1.250)	0.107	/	/
Gender (Male)	0.543(0.032-9.176)	0.672	/	/
CCI	1.191(0.702-2.021)	0.518	/	/
Day 1 BISAP	38213278(0.000-/)	0.995	/	/
Day 1 SIRS	0.941(0.157-5.641)	0.947	/	/

	Obesity	0.000(0.000-/)	0.999	/		/

505 OR=Odds Ratio, CI=Confidence Interval, CCI=Charlson Comorbidity Index, BISAP=Bedside

506 Index for Severity in Acute Pancreatitis Sequential, SIRS= Systemic Inflammatory Response

507 Syndrome.

508

509 **Table 6 Binomial Logistic regression analysis for in-hospital mortality among intensive care**

510 **patients with acute pancreatitis**

	Univariable		Multivariable	
	OR（95% CI）	*p*	OR（95% CI）	*p*
Age	1.036(1.024-1.048)	<0.001	1.001(0.985-1.017)	0.912
Gender (Male)	0.820(0.572-1.175)	0.279		
CCI	1.268(1.194-1.347)	<0.001	1.204(1.117-1.298)	<0.001
Day 1 BISAP	2.484(2.010-3.071)	<0.001	1.710(1.321-2.213)	<0.001
Day 1 SIRS	1.690(1.349-2.116)	<0.001	1.710(1.321-2.213)	<0.001
Obesity	0.625(0.489-1.536)	0.625		
RAP	0.228(0.055-0.947)	0.042	0.380(0.088-1.637)	0.194

511 OR=Odds Ratio, CI=Confidence Interval, CCI=Charlson Comorbidity Index, BISAP=Bedside

512 Index for Severity in Acute Pancreatitis Sequential, SIRS= Systemic Inflammatory Response

513 Syndrome, RAP= Recurrent Acute Pancreatitis.

514

515

516 **Table 7 Comparison of ROC curves (initial acute pancreatitis)**

|	AUC	95%CI	Optimal cut-off	Sensitivity (%)	Specificity (%)	Youden's index
BISAP	0.720	0.691~0.748	>2	77.94	56.92	0.3486
LODS	0.847	0.823~0.869	>6	82.35	75.89	0.5825
OASIS	0.808	0.781~0.832	>36	77.94	71.48	0.4942
SAPS II	0.845	0.820~0.867	>43	75.00	79.00	0.5400

517 ROC=Receiver Operating Characteristic, AUC=Area Under Curve, BISAP=Bedside Index for

518 Severity in Acute Pancreatitis, LODS=Logistic Organ Dysfunction System, OASIS=Oxford Acute

519 Severity of Illness Score, SAPS II=Simplified Acute Physiology Score II.

520

521 **Table 8 Comparison of ROC curves (recurrent acute pancreatitis)**

	AUC	95%CI	Optimal cut-off	Sensitivity (%)	Specificity (%)	Youden's index
BISAP	0.944	0.849~0.988	>3	100.0	88.89	0.8889
LODS	0.861	0.743~0.939	>7	100.0	81.48	0.8148
OASIS	0.681	0.542~0.799	>27	100.0	50.00	0.5000
SAPS II	0.829	0.704~0.916	>33	100.0	68.52	0.6852

522 ROC=Receiver Operating Characteristic, AUC=Area Under Curve, BISAP=Bedside Index for

523 Severity in Acute Pancreatitis, LODS=Logistic Organ Dysfunction System, OASIS=Oxford Acute

524 Severity of Illness Score, SAPS II=Simplified Acute Physiology Score II.

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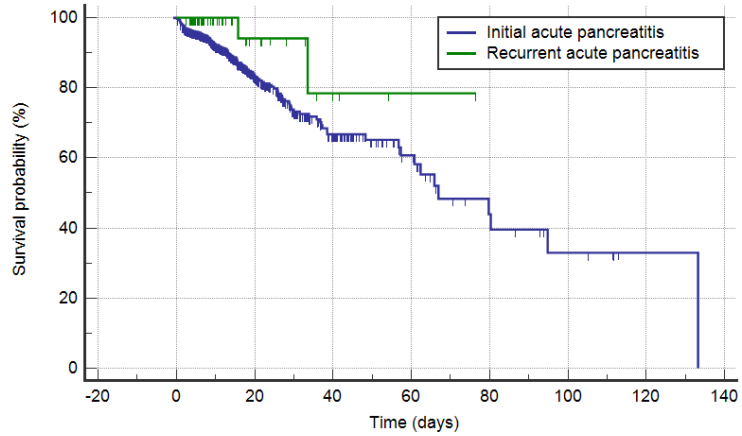
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527 **Figure 1 Kaplan-Meier curves of patients with initial and recurrent acute pancreatitis in the**
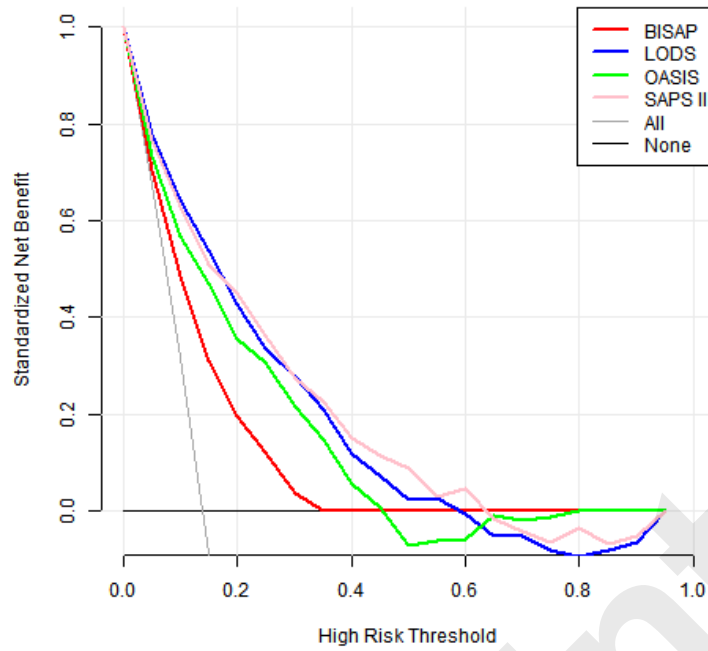528 **intensive care unit**
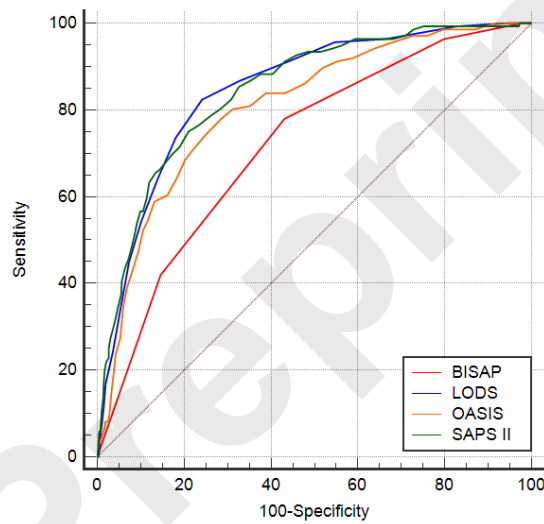
529
530 **Figure 2 ROC curves of four scoring systems for predicting in-hospital mortality in initial**
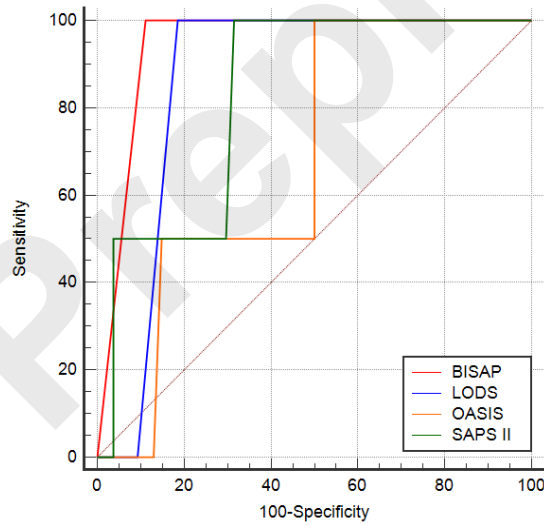531 **acute pancreatitis**

532

Figure 3 DCA curves of four scoring systems for predicting in-hospital mortality in initial acute pancreatitis
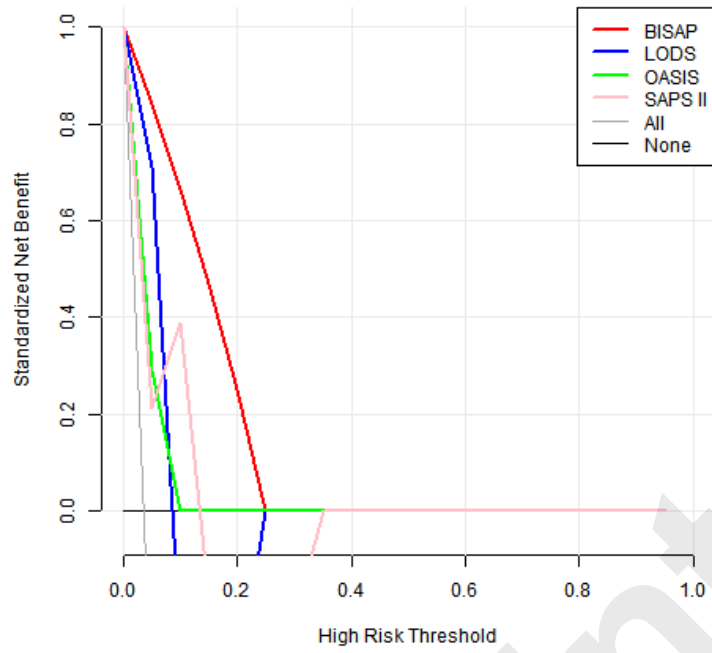

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Figure 4 ROC curves of four scoring systems for predicting in-hospital mortality in recurrent acute pancreatitis
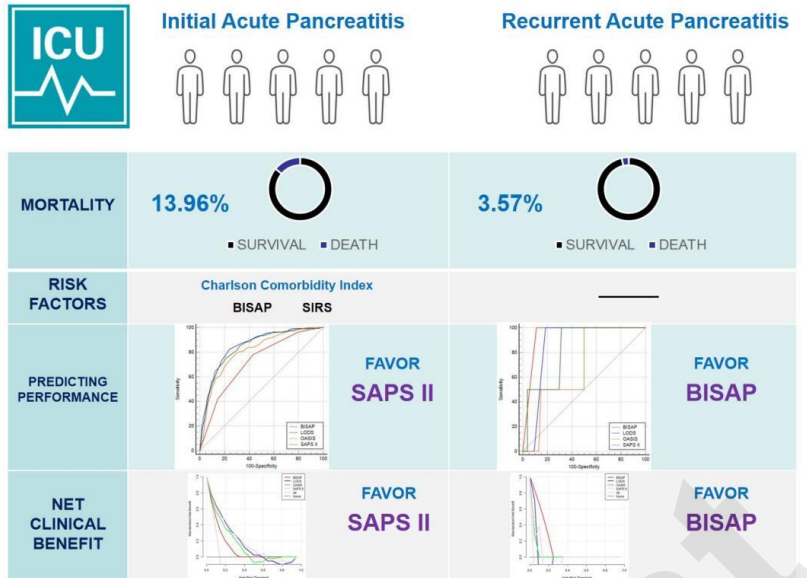
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**Figure 5 DCA curves of four scoring systems for predicting in-hospital mortality in
recurrent acute pancreatitis**

539
540

Take-home messages

1.The in-hospital mortality rate was 13.96% in patients with IAP and 3.57% in patients with RAP.

2. For IAP, the Charlson comorbidity index, BISAP score, and SIRS score were independent risk factors for in-hospital mortality.

3. The SAPS II score was a better scoring system for predicting in-hospital mortality in patients with IAP.

4. The BISAP score showed potential for predicting in-hospital mortality in patients with RAP.

Legends

ICU, Intensive Care Unit

BISAP, Bedside Index for Severity in Acute Pancreatitis

SIRS, Systemic Inflammatory Response Syndrome

SAPS II, Simplified Acute Physiology Score II

LODS, Logistic Organ Dysfunction System

OASIS, Oxford Acute Severity of Illness Score