Random Blood Glucose Level to Predict Gallstone Pancreatitis Severity in Indonesian Patients

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Abstract. Established gallstone pancreatitis severity predictors are impractical because they require multiple diagnostic variables that take time to develop. This study aimed at finding a simple severity predictor to improve patient management. We conducted this cross-sectional study by extracting data from the medical records of patients with gallstone pancreatitis (ICD 10 code K85.1) in the Cipto Mangunkusumo Hospital during 2008–2016. For statistical analysis, we used random blood glucose (RBG) levels on admission, severity grading based on the 2012 revision of the Atlanta Classification, and mortality. Data included were from 41 patients with gallstone pancreatitis [mean age, 49.2 years; men, 24 (58.5%) and women, 17 (41.5%)]. The median RBG levels in mild, moderately severe, and severe disease groups were 109.5; 131; and 171 mg/dL, respectively. This study found a significant difference in RBG level between patients in the mild and those in the severe disease groups (P = 0.008). ROC curve of RBG and severe gallstone pancreatitis revealed an area under the curve (AUC) of 0.885 (CI 95%, 0.743–1.000). RBG level at 154.5 mg/dL had the optimal sensitivity (75%) and specificity (91.8%) values to predict severe disease. The positive and negative predictive values at the cutoff RBG level of 154.5 mg/dL were 50% and 97.1%, respectively. This study found no association between RBG level and mortality but found an association between severity grading and mortality (P = 0.021; OR 0.028). RBG level can be used to accurately predict gallstone pancreatitis severity.

1. Introduction

Approximately 10%–20% of patients with acute gallstone pancreatitis develop a severe disease with systemic inflammation, organ failure, and death [1]. Failure to predict severe gallstone pancreatitis leads to under-treatment and increased morbidity and mortality [2]. The established severity predictors, such as Ranson, modified Glasgow, and APACHE II scores are not convenient because they usually require several days and multiple diagnostic tests before giving results [2]. Therefore, a simple severity predictor is needed for quick and early predictions, particularly in referral hospitals like ours, wherein patients arrive with late presentations of the disease.

Various single predictors have been studied to predict severe gallstone pancreatitis on admission; one of them is the random blood glucose (RBG) level. Increasing RBG levels in patients with acute gallstone pancreatitis not diagnosed with diabetes mellitus indicate severe islet cell damage [2,3]. This
test is simple, cheap, and readily available. We conducted this study to evaluate the use of RBG as a single gallstone pancreatitis severity predictor.

2. Materials and Methods
This was a retrospective cross-sectional study to establish the role of RBG as an acute gallstone pancreatitis severity and mortality predictor. Data were obtained from the medical records of patients with acute gallstone pancreatitis (ICD 10 code K85.1) admitted during 2008–2016 to the Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Patients with previously diagnosed diabetes mellitus were excluded. Data on demographics, RBG level on admission, severity grading based on the Atlanta Classification 2012 revision, and mortality were recorded. Statistical analysis was performed using SPSS 20.0 software to find the associations between RBG levels and severity grading, between RBG levels and mortality, and between severity grading and mortality. Association was identified when the P-value was <0.05. This study had been approved by Ethical Committee of Health Research at Faculty of Medicine, Universitas Indonesia and Cipto Mangunkusumo Hospital.

3. Results
This study found 140 patients with acute pancreatitis, and 46 (32.9%) of them had biliary etiologies. Of them, only 41 patients met the inclusion criteria and did not present exclusion criteria. Mean age of the patients was 49.2 years (+13.1 years); 24 patients (58.5%) were men and 17 (41.5%) were women. We found 30 (75%) patients had mild biliary pancreatitis, 7 (17.1%) had moderately severe disease, and 4 (7.9%) had severe disease. The median of RBG levels in the mild, moderately severe, and severe disease groups were 109.5 (80–168) mg/dL, 131 (84–186) mg/dL, and 171 (122–183) mg/dL, respectively.

Most patients with moderately severe gallstone pancreatitis had kidney dysfunction. Local complications were assessed in 3 patients who underwent pancreatic computed tomography (CT) and the findings were as follows: 1 patient with acute peripancreatic fluid collection (APFC), 1 patient with acute necrotic collection (ANC), and 1 patient with pancreatic edema. Of the 4 patients with severe disease, 2 had kidney dysfunction, 1 had respiratory dysfunction, and 1 had multiple organ dysfunction syndrome (MODS). Two patients underwent abdominal CT scans and were found to have APFC and ANC (Table 1).

| Types of complications | Severity grading |
|------------------------|------------------|
|                        | Moderately severe (n = 7) | Severe (n = 4) |
| **Local complication** |                  |                |
| Acute peripancreatic fluid collections (APFCs) | 1 | 1 |
| Pancreatic pseudocyst | - | - |
| Acute necrotic collections (ANCs) | 1 | 1 |
| Walled-off necrosis | - | - |
| **Systemic complication** |                  |                |
| Respiratory dysfunction | 1 | 1 |
| Kidney dysfunction | 4 | 2 |
| Cardiovascular dysfunction | - | - |
| Exacerbation of comorbidity | 1 | - |
| Multiple organ dysfunction syndrome (MODS) | - | 1 |
Only 7 (17.1%) out of 41 patients had been assessed for severity by the treating physicians, using multivariable tools. Two patients with Ranson score of 0 (RBG 98 mg/dL and 161 mg/dL) had mild gallstone pancreatitis; 2 patients with Ranson scores of 3 (RBG 84 mg/dL) and 4 (RBG 145 mg/dL) had moderately severe gallstone pancreatitis; and one patient with Ranson score of 4 (RBG 183 mg/dL) had severe disease. The severe gallstone pancreatitis patient with Ranson score of 4 (RBG 183 mg/dL) eventually died. One patient with BISAP score of 0 (RBG 115 mg/dL) had mild gallstone pancreatitis and 1 patient with BISAP score of 2 (RBG 131 mg/dL) had a transient kidney failure.

Overall, 3 patients died; 2 of them had severe disease (the causes of deaths were respiratory failure and MODS) and 1 patient had mild gallstone pancreatitis and died from a post-cholecystectomy complication.

We found a significant difference in the median RBG levels among the three severity groups (P = 0.029). Post hoc analysis revealed that only mild and severe disease presented a significant difference of the median RBG level with a P-value of 0.008 (Table 2).

Table 2. Differences in the median RBG level in each severity group.

| Severity Degree          | Median (mg/dL) | P-value   |
|--------------------------|----------------|-----------|
| Mild                     | 109.5 (80–168) | 0.029<sup>a</sup> |
| Moderately severe        | 131 (84–186)   |           |
| Severe                   | 171 (122–183)  |           |
| Mild–moderately severe   |                | 0.404<sup>b</sup> |
| Moderately severe–severe |                | 0.186<sup>b</sup> |
| Mild–severe              |                | 0.008<sup>b</sup> |

Note: <sup>a</sup>Kruskal–Wallis; <sup>b</sup>Mann–Whitney

ROC curve analysis of RBG level to predict severe disease revealed an area under the curve (AUC) of 0.885 (95% CI, 0.743–1.000) (Figure 1). The optimal sensitivity (75%; 95% CI 30.06–95.44) and specificity (91.9%; 95% CI 78.7–97.2) were found at an RBG level of 154.5 mg/dL, with a positive predictive value (PPV) of 50% (95% CI, 18.76–81.24) and negative predictive value (NPV) of 97.1% (95% CI, 85.47–99.49). Further analyses found that RBG levels between 150 and 154.5 mg/dL had the same value of sensitivity, specificity, PPV, and NPV.
Figure 1. ROC curve of RBG level and severe gallstone pancreatitis revealed an AUC of 0.885 with 95% CI of 0.743–1.000. ROC: receiver operating characteristic; RBG: random blood glucose; AUC: area under the curve; CI: confidence interval.

Despite the difference between the median RBG level in patients who survived and that in those who eventually died, Mann–Whitney test revealed no significant association between RBG level and mortality (P = 0.249). However, we found a significant association between severity degree and mortality (P = 0.021; OR = 0.028) using a Fisher exact test.

4. Discussion
The association between RBG level and severity grading has been believed to be caused by damage to islet cells, which eventually decreases the insulin synthesis and increases the glucagon levels [4]. Patients with acute pancreatitis have been shown to present fasting hyperglycemia, hyperglucagonemia, and relative hypoinsulinemia at 48–72 h after disease onset, and the values gradually get normalized after 15 days. Hyperglycemia can also occur due to the critical condition and sepsis [5]. Factors that worsen hyperglycemia in critically ill patients are as follows: increased production of hepatic glucose and decreased uptake of glucose by peripheral tissues [6].

Cellular inflammatory mediators and the hypothalamic–pituitary–adrenal axis get activated in critically ill patients in response to the stress. The release of cortisol, catecholamines, glucagon, and growth hormone leading to protein and lipid breakdown are factors reflecting adaptation to illness and stress. Inadequate systemic insulin levels, insulin resistance due to counter regulatory hormones secretion, and negative effects of hyperglycemia lead to patients’ deterioration. High blood glucose levels can cause mitochondrial injury by releasing reactive oxygen species and endothelial dysfunction by hampering nitric oxide production. Therefore, persistent stress-induced hyperglycemia can worsen the clinical outcome and increase the mortality. Maintaining normoglycemia in ICU patients not having diabetes using insulin therapy can prevent severe nosocomial infections and lethal sepsis [5,6].

Studies have found that the presence of diabetes mellitus decreases the prognostic accuracy of blood glucose levels. Ranson excluded the blood glucose level as a prognostic factor in patients with diabetes mellitus, and Meek et al. proved that blood glucose does not play a role as a predictor in patients with diabetes mellitus. On a study of patients with acute pancreatitis due to various etiologies, Fan et al. found that diabetes increased the false positive results [2-7]. The present study had 5 (11%) patients with gallstone pancreatitis with known diabetes mellitus, and we excluded them from the study to minimize bias.

Studies have evaluated RBG level ≥ 150 mg/dL as a gallstone pancreatitis severity or mortality predictor with a sensitivity of 79%–89.3% and a specificity of 79%–85% by measuring the following outcomes: development of local or systemic complications, the need for ICU monitoring, and mortality [2-8-11]. Unlike those studies, the present study sought to find the appropriate RBG cutoff level in a local setting. Our ROC curve analysis found the AUC to be 0.885 with 95% CI of 0.743–1.000, which indicates that RBG level is useful as an accurate severe gallstone pancreatitis predictor despite analyzing only 4 severe cases in this study. The optimal sensitivity and specificity were obtained at an RBG level of 154.5 mg/dL. Our sensitivity showed that an RBG level ≥ 154.5 mg/dL can predict 75% patients with severe disease. The PPV showed that only 50% of patients with RBG levels ≥ 154.5 mg/dL have severe disease. The specificity showed that 91.9% patients with mild to moderately severe disease will have RBG levels < 154.5 mg/dL. The NPV showed that 97.1% of patients with RBG < 154.5 mg/dL do not have severe disease. However, good ranges of 95% confidence intervals were obtained on specificity (CI 95% 78.7–97.2) and NPV (CI 95% 85.47–99.49). Therefore, RBG levels < 154.5 mg/dL can be used to predict non-severe disease. Our results are consistent with those of other studies that used an RBG level of 150 mg/dL as the cutoff point for severe gallstone pancreatitis predictor.

Among the 5 patients who had a calculated Ranson score, 1 showed a disagreement between the Ranson score and RBG level in terms of severity. The Ranson score was 0 and the patients was categorized as having mild disease, but RBG level was 161 mg/dL. Based on this one case, the Ranson
score was superior to RBG level alone. Only 2 patients had calculated BISAP scores, and the scores accurately predicted the occurrence of organ failure. These 2 patients had mild and moderately severe disease. Both patients had RBG < 154.5 mg/dL and none of them developed severe gallstone pancreatitis. Therefore, RBG level agreed with the BISAP score in this study.

This study found no association between RBG level and mortality of patients with gallstone pancreatitis despite the large median gap between the survivors and the non-survivors. This result contradicts the results of a study by Rajaratnam et al. that found that an RBG ≥ 150 mg/dL predicts mortality with comparable likelihood ratio to the APACHE II score, with a sensitivity of 88% [11]. At the same time, a study by Falciglia et al. also found that the risk of mortality increases in accordance with RBG level [12]. In the present study, 1 patient who died due to a post-cholecystectomy complication had mild gallstone pancreatitis with a low RBG level. This possibly explains the insignificant association between RBG level and the mortality in our study.

There was an association between severity degree and mortality, indicating that the patients with mild and moderately severe gallstone pancreatitis had 0.028 times the mortality risk of severe gallstone pancreatitis patients. The mortality rate of severe gallstone pancreatitis patients in this study was 50%, which is consistent with that in other studies having mortality rates of 45%–100% [13].

A normal blood glucose level should be maintained to decrease the mortality risk as well as avoid episodes of hypoglycemia. Van den Berghe found that patients with RBG levels of 110–150 mg/dL (post-insulin treatment) had a lower mortality risk than those with RBG levels of 150–200 mg/dL, and Falciglia et al. found that RBG levels of 111–145 mg/dL displayed the lowest OR toward mortality [5-12].

5. Conclusion
RBG level on admission in patients with gallstone pancreatitis can predict disease severity with good accuracy. We suggest that patients with RBG ≥ 154.5 mg/dL be monitored closely and treated aggressively to decrease morbidity. Maintaining RBG level below 150 mg/dL may also be beneficial.

References
[1] Park J Y, Jeon T J, Ha T H, Hwang J T, Sinn D H, Oh T H, Shin W C and Choi W C 2013 Bedside index for severity in acute pancreatitis: comparison with other scoring systems in predicting severity and organ failure Hepatobil. Pancreat. Dis. Int. 12 645-50.
[2] Meek K, Toosie K, Stabile B E, Elbassir M, Murrell Z, Lewis R J, Chang L, de Virgilio C 2000 Simplified admission criterion for predicting severe complications of gallstone pancreatitis Arch. Surg. 135 1048-52.
[3] Working Group IAP/APA Acute Pancreatitis Guidelines 2013 IAP/APA evidence-based guidelines for the management of acute pancreatitis Pancreatol. 13, e1-15.
[4] Solomon S S, Duckworth W C, Jallepalli P, Bobal M A and Iyer R 1980 The glucose intolerance of acute pancreatitis: hormonal response to arginine Diabetes. 29 22-6.
[5] Van den Berghe G. 2004 How does blood glucose control with insulin save lives in intensive care? J. Clin. Invest. 114 1187-95
[6] Xiu F, Stanojcic M, Diao L and Jeschke M G 2014 Stress hyperglycemia, insulin treatment, and innate immune cells Int. J. Endocrinol. 2014 486403.
[7] Fan S T, Lai E C, Mok F P, Lo C M, Zheng S S, Wong J 1993 Prediction of the severity of acute pancreatitis Am. J. Surg. 166 262-8
[8] Kasimu H, Jakai T, Qilong C and Jielile J 2009 A brief evaluation for pre-estimating the severity of gallstone pancreatitis JOP 10 147-51.
[9] Arnell T D, de Virgilio C, Chang L, Bongard F and Stabile B E 1996 Admission factors can predict the need for ICU monitoring in gallstone pancreatitis Am. Surg. 62 815-9
[10] Singh K, Nain P, Matta H, Ohri A, Chaudhry A, Jain M 2005 Simplified criteria for predicting the severity of gallstone pancreatitis Indian J. Surg. 67 135.
[11] Rajaratnam S G and Martin I G 2006 Admission serum glucose level: an accurate predictor of
outcome in gallstone pancreatitis *Pancreas* **33** 27-30

[12] Falciglia M, Freyberg R W, Almenoff P L, D’alessio D A, Render M L 2009 Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis *Crit. Care Med.* **37** 3001.

[13] West D M, Adrales G L and Schwartz R W 2002 Current diagnosis and management of gallstone pancreatitis *Current Surg.* **59** 296-8.