DETERMINATION OF 30-DAY MORTALITY IN PERFORATED PEPTIC ULCER BASED ON THREE EXISTING SCORING SYSTEMS - 5-YEAR RETROSPECTIVE REVIEW IN HOSPITAL SULTANAH NURZAHIRAH FROM JANUARY 2014 TO DECEMBER 2018

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LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologist
AUC	Area under the curve
COPD	Chronic obstructive pulmonary disease
DVT	Deep vein thrombosis
HIS	Hospital Information System
HSNZ	Hospital Sultanah Nurzahirah
ICD	International Classification of Disease
IHD	Ischaemic Heart Disease
MPI	Mannheim Peritonitis Index
NPV	Negative Predictive Value
NSAIDS	Non-steroidal anti-inflammatory drugs
PPU	Perforated Peptic Ulcer
PPV	Positive Predictive Value
PULP	Peptic Ulcer Perforation
ROC	Receiver operating curve
USM	Universiti Sains Malaysia

ABSTRAK

Latar belakang: Ulser peptik berlubang mempunyai kadar morbiditi dan kematian yang tinggi. Sistem skor yang sedia ada untuk mengelaskan pesakit berisiko kematian adalah skor-skor *American Society of Anasthesiologists* (ASA), Boey dan *Peptic Ulcer Perforation* (PULP). Tujuan kajian ini adalah untuk mengenalpasti kadar kematian 30 hari bagi pesakit ulser peptik berlubang yang dibedah di Hospital Sultanah Nurzahirah, dan tujuan kedua adalah untuk mengenalpasti ketepatan ketiga-tiga sistem skor tersebut.

Kaedah: Ini merupakan kajian retrospektif bagi pesakit yang dibedah untuk ulser peptik berlubang di hospital berpakar tertiari di Terengganu dari bulan Januari 2014 hingga Disember 2018. Data klinikal dan rekod pembedahan dikumpul. Kepekaan, kekhususan dan area di bawah lengkungan *receiver operating curve* (AUC) dibandingkan di antara ketiga-tiga skor tersebut.

Keputusan: Seramai 120 pesakit telah dimasukkan ke dalam kajian ini yang mana 39 orang (21.5%) meninggal dunia dalam 30 hari. Saiz ulser (p=0.039), lokasi ulser (p=0.003), jenis pembedahan (p=0.001), kebocoran (p=0.005) dan koleksi abdomen (p=0.001) berkait secara signifikan dengan kematian. Di antara sistem-sistem skor, ASA mempunyai kebolehan menjangka kematian yang terendah (AUC 0.605), sementara Boey dan PULP mempunyai kebolehan menjangka kematian sederhana dengan masing-masing mempunyai AUC 0.686 dan 0.684.

Kesimpulan: ASA, Boey dan PULP mempunyai ketepatan yang sederhana untuk menjangka kematian dalam 30 hari bagi ulser peptik berlubang, dengan ASA mempunyai kebolehan menjangka yang terendah.

ABSTRACT

Determination of 30-day mortality in perforated peptic ulcer based on three existing scoring systems– 5-year retrospective review in Hospital Sultanah Nurzahirah from January 2014 to December 2018

Background: Perforated peptic ulcer has a high morbidity and mortality. Existing scoring systems to stratify patient at risk of mortality are American Society of Anasthesiologists (ASA), Boey and Peptic Ulcer Perforation (PULP) scores. The aim of this study was to determine 30-day mortality for perforated peptic ulcer patients operated in Hospital Sultanah Nurzahirah and secondary aim was to determine the accuracy of the three scoring systems.

Methods: This is a retrospective review of patients surgically treated for perforated peptic ulcer in a tertiary hospital in Terengganu from January 2014 to December 2018. Clinical data and operative details were collected. Sensitivity, specificity, and area under the receiver operating curve (AUC) were compared between each scoring systems.

Results: A total of 120 patients were included in this study of which 39 (32.5%) died within 30 days. Size of ulcer (p=0.039), site of ulcer (p=0.003), operation type (p=0.001), leakage (p=0.005) and abdominal collection (p=0.001) were significantly associated with mortality. Among the scoring systems, ASA has lowest predictive value for mortality (AUC 0.605) while Boey and PULP has similar moderate predictive value for mortality with AUC of 0.686 and 0.684 respectively.

Conclusion: ASA, Boey and PULP has similar moderate accuracy to predict 30-day mortality in PPU, with ASA has the lowest predictive value.

CHAPTER 1: INTRODUCTION

Peptic ulcer disease which includes gastric ulcer and duodenal ulcer is known to have high morbidity and mortality worldwide. Perforation is the second most frequent complication after bleeding[1]. Population-based studies reported substantial mortality rates for perforated peptic ulcer (PPU), ranging from as low as 0.7% [2] to 27% [3].

Many scoring systems are being used to predict mortality in PPU, but not many were developed specifically for PPU. Over the years however a few scoring systems have been developed to predict mortality in PPU.

One of the previous scoring systems used in PPU was Mannheim Peritonitis Index (MPI). It was developed for patients presented with peritonitis and comprises of both pre-operative and post-operative components[4]. ASA, Boey and PULP scoring systems have components that can be scored pre-operatively.

American Society of Anaesthesiologists (ASA) score was introduced in 1941[5] and was not specifically developed for PPU. However, it is most used by anaesthesiologist to stratify patients undergoing emergency surgery. It has been criticized for its subjectivity and wide inter-observer variability[6]. A study mortality in PPU patients with ASA score ≤ 2 was 4% while in score >2, the reported mortality was 10%[7].

Boey score was the first scoring system that directly aimed at mortality prediction for PPU[8]. In the original study, risk factors of patient were scored as zero (0), one (1), two (2) or three (3) with mortality risk of 0%, 10%, 45% and 100% respectively[8]. Multiple studies have since re-evaluated Boey score without being able to fully replicate the convincing original result[9]. Boey score was also appears to have the poorest discriminatory ability of survival[10]. Mortality risk were reported to be 10% in Boey score ≤1 and 14% in score >1[7]. In Malaysia, recently published data reported patients with risk score of zero (0), one (1), two (2) and three (3) has mortality of 0%, 24%, 44% and 32% respectively[11].

Peptic Ulcer Perforation (PULP) score is the most recent scoring system developed to predict 30-day mortality in patients operated for PPU[12]. It has seven components with a total score from 0 to maximum of 18 [12]. The original study reported 30-day mortality of 27% and further divided the patients into low-risk (score ≤7) and high-risk (score >7), with result of less than 25% mortality in score ≤7 and more than 25% in score >7 [12]. In Singapore, it is reported that there is 9% mortality in low-risk group and 15% in high-risk group [7].

While mortality of PPU is considerably high in most surgical centres, mortality risk for PPU patients in HSNZ have not been studied. On top of that, at present, clinical prediction scoring systems for mortality in PPU are not routinely used in clinical practice in our centre and other tertiary hospitals in this region. It is imperative to stratify patients ideally pre-operatively into risk categories to provide optimal care and allocate resources. An effective and reliable scoring systems would no doubt be beneficial in reducing high mortality rate

associated with PPU. To our best of knowledge, no study has been done in this region on evaluation of multiple scoring systems for mortality prediction in PPU.

The aim of this study was to determine 30-day mortality of PPU patients operated in HSNZ. Our secondary objectives were to determine the sensitivity and specificity of the three existing mortality risk scoring systems for PPU in HSNZ, and to study the demographic variables of the patients included in the study.

CHAPTER 2: MANUSCRIPT

2.1 Title, Authors and Affiliations

Determination of 30-day mortality in perforated peptic ulcer based on three existing scoring systems - 5-year retrospective review in Hospital Sultanah Nurzahirah from January 2014 to December 2018

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2.2 Abstract

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Conclusion: ASA, Boey and PULP has similar moderate accuracy to predict 30-day mortality in PPU, with ASA has the lowest predictive value.

Keywords: Perforated peptic ulcer, ASA, Boey, PULP, mortality

2.3 Introduction

Peptic ulcer disease which includes gastric ulcer and duodenal ulcer is known to have high morbidity and mortality worldwide. Perforation is the second most frequent complication after bleeding[1]. Population-based studies reported substantial mortality rates for perforated peptic ulcer (PPU), ranging from as low as 0.7% [2] to 27% [3].

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mortality rate associated with PPU. To our best of knowledge, no study has been done in this region on evaluation of multiple scoring systems for mortality prediction in PPU.

The aim of this study was to determine 30-day mortality of PPU patients operated in HSNZ. Our secondary objectives were to determine the sensitivity and specificity of the three existing mortality risk scoring systems for PPU in HSNZ, and to study the demographic variables of the patients included in the study.

2.4 Methods

2.4.1 Research design

This is a retrospective review of PPU patients operated in Hospital Sultanah Nurzahirah Terengganu. The study is registered with National Medical Research Registry, and The Human Research Ethics Committee of USM approved the study.

2.4.2 Study population

Reference population: Patients presented with PPU in HSNZ, Kuala Terengganu

Target population: Patients diagnosed with and operated for perforated peptic ulcer in HSNZ

Source population/sampling pool: Patients diagnosed with and operated for perforated peptic ulcer in HSNZ from 1st January 2014 to 31st December 2018

Sampling frame: Patients diagnosed with and operated for perforated peptic ulcer in HSNZ from 1st January 2014 to 31st December 2018 who fulfil the study criteria

Patients were identified from HSNZ electronic database (Hospital Information System – HIS) using:

1. ICD-10 (International Statistical Classification of Disease 10) diagnostic codes for
   1.1. Gastric ulcer (K25, subcategories K25.1, K25.2, K25.5, K25.6)
   1.2. Duodenal ulcer (K26, subcategories K26.1, K65.2, K26.5, K26.6).
2. Operation codes for laparotomy, Graham patch, simple closure, omental patch, gastrectomy
3. Pre- or post-operative diagnosis of perforated gastric ulcer and perforated duodenal ulcer

2.4.3 Subject criteria

Inclusion criteria

1. Patients with intraoperatively confirmed perforated peptic ulcer either duodenal or gastric

Exclusion criteria

1. Had perforations of other organs
2. Histopathology of malignant perforated tumours
3. Pregnant or breastfeeding
4. Less than 18 years of age
5. Incomplete or missing data

2.4.4 Main outcome measure

The main outcome measured was mortality, which is death occurring within 30 days of surgery, independent of the causation.

2.4.5 Operational definitions

Perforated peptic ulcer (PPU): includes both perforated duodenal and perforated gastric ulcers.

2.4.6 Three existing scoring systems

We calculated three clinical scoring systems for each patient. ASA score was based on patient's pre-existing co-morbidity, which takes into consideration the present clinical condition at admission[2]. The score is graded as 1-5 which towards higher grade denotes a normal healthy patient, patient with mild systemic disease, patient with severe systemic disease that is constant threat to life and moribund patient who is not expected to survive without the operation[7][13]. We stratify ASA score >2 as high risk for mortality, based on the experience reported from the PULP study[7][12].

Boey score was calculated based on three variables: time from onset of abdominal pain (≤24 or >24 hour), pre-operative systolic blood pressure of <90mmHg and presence od any one or more systemic illness such as heart disease, liver disease, renal disease, and diabetes mellitus[7][8]. Score of 0 carries 0% mortality risk, score of 1 carried 10% mortality risk, score of 2 carries 45.5% mortality risk and score of 3 carries 100% mortality risk. Based on this we stratify score of >1 as high risk[8].

PULP score is a seven-variable score which ranges from 0 to 18. The variables include age >65 years, active malignant disease/AIDS, liver cirrhosis, concomitant use of steroids, shock on admission, time from perforation to admission >24hours, serum creatinine >130mmol/L and ASA score[12]. Following the PULP study, we stratify score of >7 as high risk with mortality of >25%.

2.4.7 Statistical analysis

The data were collected on an excel sheet and then converted to SPSS version 24.0 9 (SPSS Inc., Chicago, IL). Chi square test was used for categorical variables, while student's t-test was used for continuous variables. P value of <0.05 was considered statistically significant. Chi square analysis was done for associations between dichotomous values.

For calculation of mortality, each scoring system was divided into 2 final categories:

1. ASA was divided into low risk (≤2) and high risk (>2)
2. Boey score was divided into low risk (≤1) and high risk (>1)
3. PULP score was divided into low risk (≤7) and high risk (>7)

To compare the three mortality risk prediction models, each scoring system was evaluated by Receiver Operating Characteristics (ROC) by plotting the score's sensitivity (y) against 1-specificity (x). This produced an Area Under the Curve (AUC) for each model. The AUC signifies each model's ability to distinguish survivors from non-survivors[14]. The optimal AUC is close to 1[10].

The probability that a patient with a positive test result dies within 30 days of surgery is reported as the positive predictive value (PPV). Likewise, the probability that a patient with a negative test result survive within 30 days of surgery is reported as negative predictive value (NPV). The optimal PPV and NPV are close to 100%[10].

2.5 Results

120 patients were included in the study. Mean age were 63 years with 63.3% aged 60 years or more. Majority (89%) of the patients were male. The 30-day mortality in this study was 32.5% (39 patients). ***Table 1*** shows the demographic profile of the patients. 31% of the patients were smokers and 27% has history of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) use. 39% has Diabetes Mellitus, 19% has chronic renal failure, 19% has ischaemic heart disease, and 4-5% has either active malignant disease, liver cirrhosis, steroid use, and chronic obstructive pulmonary disease (COPD). Emergency laparotomy was done in all patients.

Table 1 Patient demography

Characteristics	**Mean (SD)**	**n=120 (%)**
Age	62.97 (17.05)	
<60		44 (36.7)
≥60		76 (63.3)
Gender		
Male		89 (74.2)
Female		31 (25.8)
Smoking history		32 (26.7)
NSAIDs use		27 (22.5)
Comorbids		
Active malignant disease		4 (3.3)
Liver cirrhosis		5 (4.2)
Steroid use		4 (3.3)
Diabetes mellitus		39 (32.5)
Chronic renal failure		19 (15.8)
Ischemic heart disease		19 (15.8)
COPD		5 (4.2)
ASA score		
≤ 2		29 (24.2)
>2		91 (75.8)
Boey score		
≤ 1		72 (60.0)
>1		48 (40.0)
PULP score		
≤ 7		75 (62.5)
>7		45 (37.5)

Operative outcomes data is summarized in ***Table 2***. 89% has ulcer size in between 0.5cm to 2cm. Majority of the ulcers were gastric ulcers (84.2%) and 15.8% were duodenal ulcers. 83.3% patients had simple omental patch repair while six patients had gastric resection. Biopsy of ulcers were performed in all patients and all were of benign histopathology. 53.3% required blood transfusion and 26.7% received total parenteral nutrition.

Table 2 Operative outcomes data

Characteristics	**n=120 (%)**
Size of ulcer	
<0.5cm	5 (4.2)
0.5-2cm	89 (74.2)
>2cm	26 (21.7)
Site of ulcer	
Gastric	101 (84.2)
Duodenal	19 (15.8)
Operation type	
Simple omental patch	106 (88.3)
Gastric resection	6 (5.0)
Others	8 (6.7)
Histopathology	
Malignant	0 (0.0)
Benign	120 (100.0)

We analysed factors associated with 30-day mortality (***Table 3***) which includes demographic data, smoking history, use of NSAIDs, comorbidities, size of ulcer, size of ulcer, type of operation and morbidities such as leakage, re-laparotomy, abdominal collection, surgical site infection (SSI) and deep vein thrombosis (DVT). We observed that size of ulcer (p=0.039), site of ulcer (p=0.003), operation type (p=0.001), leakage (p=0.005) and abdominal collection (p=0.001) were significantly associated with mortality.

Table 3 Factors associated with 30-day mortality

Factors		Alive	Death	p-value
Age	<60	33	11	0.128
	≥60	48	28	
Gender	Male	61	28	0.664
	Female	20	31	
Smoking		22	10	0.552
NSAIDs use		18	9	0.545
Malignant disease		2	2	0.392
Liver Cirrhosis		2	3	0.193
Steroid use		3	1	0.608
Diabetes Mellitus		22	17	0.057
Renal Failure		12	7	0.423
Ischaemic heart disease		11	8	0.237
COPD		3	2	0.525
Size of ulcer	<0.5cm	5	0	0.039
	0.5-2cm	63	26	
	>2cm	13	13	
Site of ulcer	Gastric	74	27	0.003
	Duodenal	7	12	
Operation type	Simple omental patch	76	30	0.001
	Gastric resection	0	6	
	Others	5	3	
Leakage		3	8	0.005
Re-laparotomy		5	6	0.099
Abdominal collection		6	12	0.001
SSI		10	4	0.499
DVT		1	2	0.246

75.8% patients had ASA score of more than 2, 40% had Boey score of more than 1 and 37.5% had PULP score more than 7. The PPV of all scoring system in predicting 30-day mortality were low: ASA score has PPV of 35.2%, Boey score of 52.1% and PULP score of 46.7%. On the other hand, NPV of all scoring system in predicting 30-day mortality were high: ASA score has NPV of 75.9%, Boey score of 80.6% and PULP score of 76%. ASA score exhibited highest sensitivity (82.1%) and Boey score exhibited highest specificity (71.6%) (***Table 4***).

Table 4 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for 30-day mortality prediction

Scoring	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ASA score >2	82.1	27.2	35.2	75.9
Boey score >1	64.1	71.6	52.1	80.6
PULP score >7	53.8	70.4	46.7	76.0

The scoring systems' accuracy indices were compared with ROC analysis (***Figure 1***). The AUCs for the Boey and PULP score were similar. Boey score has AUC of 0.686 (p=0.001, CI 0.580-0.793) while PULP score has AUC of 0.684 (p=0.001, CI 0.580-0.793). ASA score shows slightly lower AUC at 0.607 (p=0.062, CI 0.498-0.712) (***Table 5***).

Table 5 Area Under the Curves (AUC) for 30-day mortality prediction

Scoring	AUC	p value	95% CI
ASA score >2	0.605	0.062	0.498-0.712
Boey score >1	0.686	0.001	0.580-0.793
PULP score >7	0.684	0.001	0.588-0.780

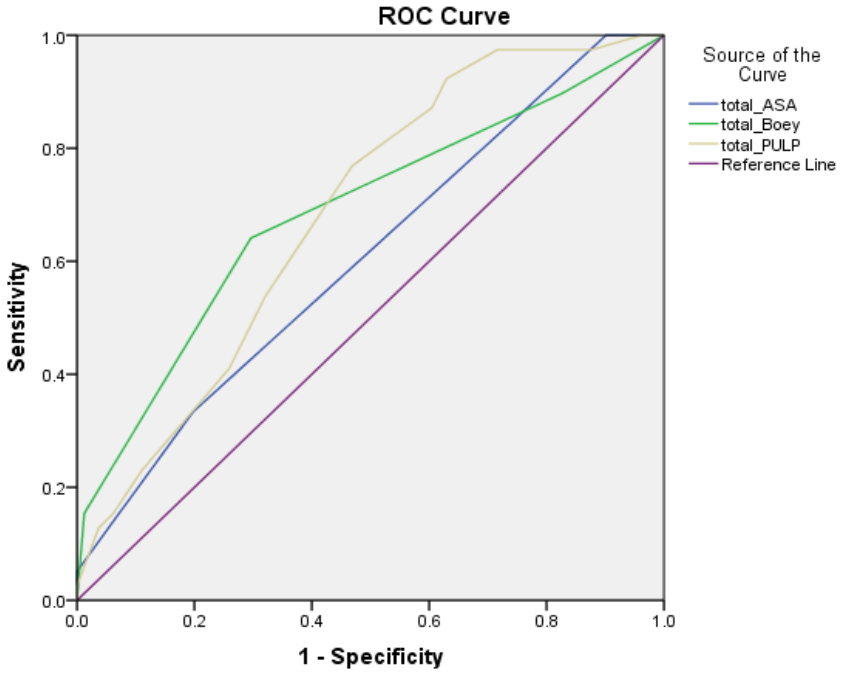

Figure 1 Receiver Operating Characteristics (ROC) curves with Area Under the Curve (AUC) for ASA, Boey and PULP scores for 30-day mortality

2.6 Discussion

Peptic ulcer disease which includes gastric ulcer and duodenal ulcer is known to have high morbidity and mortality worldwide. Perforation is the second most frequent complication after bleeding[1]. In present study, the 30-day mortality post PPU repair is 32.5%. It is also noted that in our study ASA score of more than 2, Boey score of more than 1, and PULP score of more than 7 had moderate predictive accuracy for mortality. ASA score of more than 2 has the lowest predictive accuracy of morality than the other two scoring systems.

Our outcome of 30-day mortality is significantly higher than those reported by other studies in Qatar (0.7%), Singapore (7.2%), Turkey (10.1%), Denmark (17%, 27%), and India (26.3% and 11%) [2][7][15][10][12][16][17]. Only one recent study in India that reported higher mortality than our study at 33.3% [18]. In present study, we observed that size of ulcer (p=0.039), site of ulcer (p=0.003), operation type (p=0.001), leakage (p=0.005) and abdominal collection (p=0.001) were significantly associated with mortality. A recent large cohort study in United Kingdom reported 90-day mortality of 10.61% most likely due to it only studying perforated duodenal ulcers only, while our study examined combinations of perforated gastric ulcers and perforated duodenal ulcers[17]. A multicentre prospective study on perforated peptic ulcer in 2011 reported a reduced 30-day mortality of 17% in hospitals who applied multimodal and multidisciplinary perioperative care protocols compared to hospitals that did not, with 30-day mortality of 27%[19]. This may be correlated with high 30-day mortality in our study, as our study centre probably did not use any of such

protocols in management of patients with PPU. There is also possibility of delay diagnosis and delay time of surgery that we did not investigate in this study that may have contributed to higher 30-day mortality rate we have observed. Many studies have suggested the adverse outcomes of delaying diagnosis and surgery in patients mortality in PPU[20][21].

The median age of 63 years, similar to another local study[11] which reported mean age of 60.5 years. A study in India reported lower mean age at 40.7 years [22] and Qatar at 37.41 years[2]. In our present study, 63.3% of the patients aged 60 years and above. This translates a higher incidence of PPU in older patients, especially in Malaysia. However, age did not significantly contribute to 30-day mortality in current study (p=0.128). A few studies demonstrated that age more than 60 years was a significant predictor for mortality[11][23]. This may be contributed by multiple co-morbids in elderly, although in our study none of the co-morbidities were significant predictor for 30-day mortality. Older patients also tend to have lower immunity and poorer nutritional status[11]. PPU is observed as more common the cohorts of patients born after the twentieth century and is less common than those born afterwards[24]. The reason behind this observation is not really known, but some studies have suggested PPU in older age relation with infection with H. pylori[25], although this association was not studied in our research.

Gastric ulcers were common in our study (84.2%). This is similar to other studies that demonstrated commonest site for PPU is gastric or antrum [26][27]. A trend towards older women having more gastric ulcers and younger men having more duodenal ulcers were observed in a study in Norway[27]. While 89% were observed to have ulcers of 0.5-2cm in

size in our study, 100% of patients with ulcer of >2cm died. In our study size of the ulcer is significantly related to 30-day mortality. With regards to type of operation, 83.3% patients had simple omental patch repair while six patients had gastric resection. Alarmingly, all patients who had gastric resection died in our series. A retrospective study reported that 41 patients underwent gastrectomy for perforated benign gastric ulcers and 24% of them died[28]. Factors that associated with higher mortality rate in gastrectomy are longer operating times, ventilation and postoperative blood transfusion [15]. It is also reported that larger size of perforation associated with increased mortality[29]. Factors that might have contributed to this outcome is possibly larger ulcer size associated with more intraabdominal contaminations and furthermore contributes to higher bacterial load thus causing sepsis and mortality.

High post-operative morbidity and mortality is associated with PPU repair. A recent study in India observed 65.3% post-operative morbidity rate in PPU[26]. This is higher than reported in literature (20-50%) [30][31]. In our present series, leakage and intraabdominal collection has a significant contribution towards mortality. Prompt diagnosis, excellent peri-operative resuscitation, good surgical technique, and diligence post-operative care play important role in reducing morbidity.

It is crucial to stratify patients ideally pre-operatively into risk categories to provide optimal care and allocate resources. An effective and reliable scoring systems would no doubt be beneficial in reducing high mortality rate associated with PPU. In our study, all three scoring systems has moderate ability to predict mortality.

Among all, ASA has the lowest discriminatory ability to predict death with AUC of 0.607. In 2012 a study in Denmark[10] reported AUC of 0.73 to predict mortality while in 2015, Menekse et al reported AUC of 0.914 for ASA. Another study reported AUC of 0.69[2]. While we observed high sensitivity (82.1%), ASA has low specificity (27.2%) for PPU. This observation was reported in another study as well[23]. Two studies reported sensitivity of ASA as 83.3% and 85.7% while specificity as 98.1% and 66% [7][23]. This wide difference in result is expected as ASA score is subjective, considers systemic illness only and it can have wide range of inter-observer discrepancies.

Our study observed similar moderate predictive capability of Boey with AUC of 0.686. This is lower than reported in a study conducted in Norway[23] and Qatar[2] where the AUC for Boey was 0.75 and 0.72. Menekse reported significantly high AUC of 0.920 for Boey[15]. Boey score excluded some important parameters such as age that are known to affect mortality[7]. Since in our series most of the patients are more than 60 years of age, this might have contributed to lower AUC observed. Boey score also has low sensitivity (64.1%) and specificity (71.6) for PPU mortality. Other studies reported similar sensitivity but higher specificity[7][23].

PULP score has been reported to have high AUC value ranging from 0.75 to 0.955 [7][15]. However, in our study we observed lower AUC for PULP which is 0.684. This translates into moderate predictive value for mortality. While PULP includes multiple comorbids and more parameters than ASA and Boey, it also includes patients with ASA 5.

Most of ASA 5 (moribound) are usually managed conservatively in clinical setting since those patients are not expected to survive with or without operation. PULP also has low sensitivity of 53.8% and specificity of 70.4%. This is comparable to another study which reported sensitivity of 62.5% and specificity of 87.3%[7].

A few limitations of this study warranted to be mentioned. This is a single centre study with 120 sample size, which could have not best represent general population. Retrospective study on its own has limitations of data collection. We tried to minimise the issue of data accuracy since patient data in our centre is collected electronically.