Risk Factors Associated with in Hospital Complication Post Gastrointestinal, Pancreatic, Hepatic Cancer Surgery: A Retrospective Case Control Study (RAPHA Study)

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ABSTRACT

Background: *This study aims to develop a scoring system that will predict in-hospital morbidity post gastrointestinal (GI), pancreatic, hepatic cancer surgery in adult patients. This study took place in De La Salle University Medical Center.*

Method: *Two hundred eighty five (285) adult patients 18 years old and above who underwent gastrointestinal, pancreatic and hepatic cancer surgery from 2010 to July 31, 2014 were included. Variables were evaluated in the univariate and multivariate analysis. Calculation of specific score from the resulting factors was performed by logistic regression analysis to develop the scoring system and to determine the best cut-off score in predicting in-hospital morbidity.*

Results: *Out of 142 patients with post-operative complications, factors significantly associated with morbidity were as follows: age ≥ 75 years ($p = 0.002$), low serum albumin ($p < 0.001$), abnormal electrocardiogram (ECG) findings ($p = 0.036$) and emergency surgery ($p < 0.001$). Calculated best cut-off score was 1.4.*

Conclusion: *The RAPHA scoring system may serve as a promising aid in predicting morbidity and mortality among patients who will undergo GI cancer surgery.*

Keywords: *gastrointestinal cancer surgery, morbidity, RAPHA score*

ABSTRAK

Latar belakang: *Penelitian ini bertujuan untuk mengembangkan sistem penilaian yang akan memprediksi morbiditas di rumah sakit pasca operasi gastrointestinal (GI), pankreas, dan kanker hati pada pasien dewasa. Penelitian ini berlangsung di De La Salle University Medical Center.*

Metode: *Dua ratus delapan puluh lima (285) pasien dewasa berusia 18 tahun ke atas yang menjalani operasi kanker gastrointestinal, pankreas dan hati dari 2010 hingga 31 Juli 2014 dimasukkan ke dalam penelitian ini. Variabel dievaluasi dalam analisis univariat dan multivariat. Perhitungan skor spesifik dari faktor-faktor yang dihasilkan dilakukan dengan analisis regresi logistik untuk mengembangkan sistem penilaian dan untuk menentukan skor cut-off terbaik dalam memprediksi morbiditas di rumah sakit.*

Hasil: *Dari 142 pasien dengan komplikasi pasca-operasi, faktor yang secara signifikan terkait dengan morbiditas, yaitu: usia ≥ 75 tahun ($p = 0,002$), albumin serum rendah ($p < 0,001$), temuan EKG yang abnormal*

(p = 0,036) dan keadaan darurat operasi (p < 0,001). Skor cut-off terbaik yang dihasilkan adalah 1,4.

Simpulan: *Sistem penilaian RAPHA dapat memberikan bantuan yang cukup baik dalam memprediksi morbiditas dan mortalitas di antara pasien yang akan menjalani operasi kanker gastrointestinal.*

Kata kunci: *operasi kanker gastrointestinal, morbiditas, skor RAPHA*

INTRODUCTION

Cancer is the third leading cause of morbidity and mortality in the Philippines. Among the top listed cancers are cancers of the oral cavity, stomach, colon, liver, and rectum. In year 1993-1995, the Department of Health- Rizal Cancer Registry (DOH-RCR) and the Philippine Cancer Society Inc.-Manila Cancer Registry (PCSI-MCR) presented that liver malignancies were more predominant with 40 individuals per 100,000 population diagnosed.[1] Worldwide, gastrointestinal (GI) malignancies remains a public health issue. Virani et al discussed the prevalence of GI tract and liver cancer.[2] Colorectal cancer (CRC) has an annual incidence of 1 million cases and an annual mortality of more than 500,000 cases. CRC is the second most common cause of cancer death followed by gastric cancer. Cancer of the pancreas is the fourth most common cancer in men and fifth most common cancer in women. It has the lowest 5-year survival rate of any gastrointestinal tumors. Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third most common cause of cancer mortality.[3]

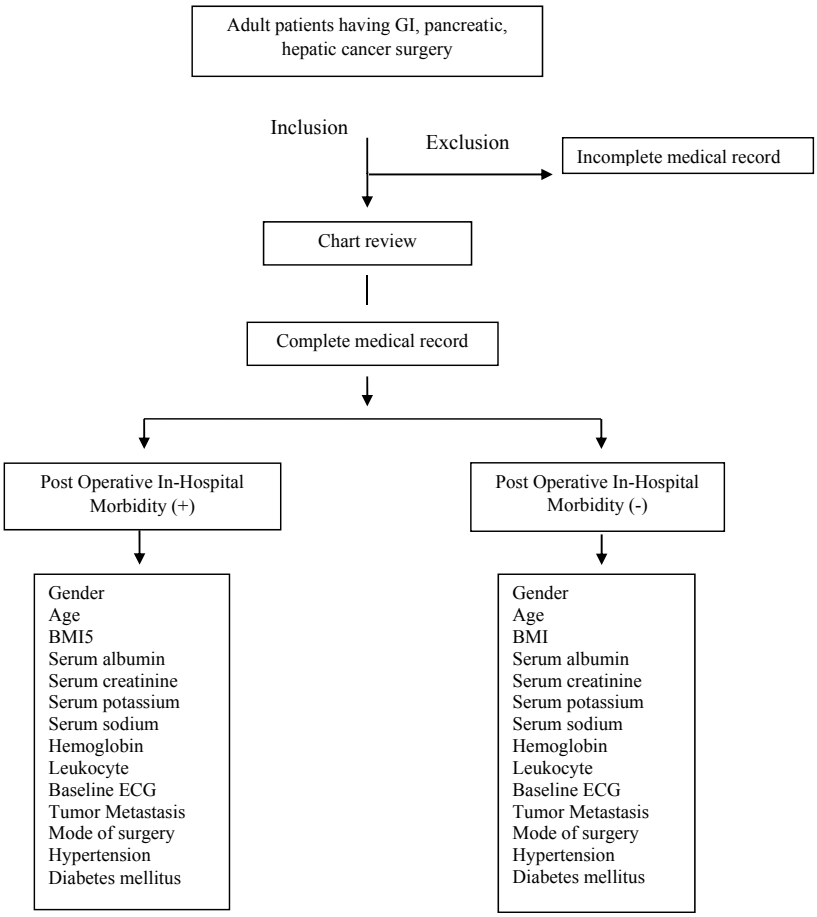
Accompanying the number of diagnosed cases of GI malignancies comes the significant number of procedures done in the surgical world. In a study done by Dikken et al done across Europe for the year 2004-2008, there were 9010 gastrectomy cases registered. In Manila, Philippines, a study by Ang et al showed thirty out of eighty one patients with gastric adenocarcinoma underwent total gastrectomy from September 1985 to June 2001.[4] Among post gastrectomy patients in New South Wales Hospital, a 4.4% overall 30-day mortality was reported by Smith et al.[5] Pancreatic surgery represents one of the most challenging areas in digestive surgery, and it has been historically associated with up to 50% morbidity and 5% mortality. Most common reported morbidity is fistula formation and collection usually related to pancreatic parenchymal transection techniques.[6] Development in surgical techniques in partial hepatectomy has enabled the performance of the procedure with operative mortality rate of less than 5% in high-volume centers in recent years. In a study by Poon et al in 2004, the overall morbidity, 30-day operative mortality, and hospital mortality were 32.4% (n = 396), 3.2% (n = 39), and 4.9% (n = 60), respectively.[7] Results varied depending on the histology of the tumor and the presence of cirrhosis.

There are several established scoring systems which are currently being utilized to assess patients for general surgery pre-operatively. Collaborative efforts from internists, surgeons and anesthesiologists has aided creating such scoring systems to assure patients safety and measure the probability of complications.[8] The Goldmann classification and Lee Revised Cardiac Risk Index were some of the pre-operative scoring used to specifically determine cardiac risk. In 2005, Bollschweiler et al evaluated the use of physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM) scoring system in patients undergoing D2 gastrectomy among gastric cancer patients.[9] This scoring system has been created by Copeland et al in 1990 as patient risk prediction model constructed on 12 patient characteristics and 6 operative characteritics. It was developed for quality assessment in general surgical units. There were modifications to assess its performance within other specific subgroups such as vascular and colorectal surgeries (V-POSSUM, CR-POSSUM).[10] Its use has also been validated to assess risks with other surgical procedures such as orthopaedic, pancreatic and gastric surgery. This scoring system includes intra-operative variables and therefore cannot completely assess patient pre-operatively. Moreover, there is no scoring system specifically used to assess possible complications of post GI, pancreas, liver cancer surgery pre-operatively. This study aims to provide specific scoring to provide pre-operative risk assessment on patients who will undergo gastrointestinal malignancy surgery.

METHOD

This is a retrospective case control study performed at a tertiary teaching hospital. A graphic outline of the study design is shown below.

The study population consisted of all adult patients (age ≥ 18 years old) having GI, pancreatic, hepatic surgery at the DLSUMC between January 1, 2010 and July 31, 2014.The data collection, processing, and



Fifure 1. Graphic outline of the study design

analysis were conducted between November 2014 and December 2015. Sample sizes were calculated based on study by Bollschweiler.[8] There was 65.7% patients who had normal postoperative courses and 34.3% morbidity rate. With a significant hazard ratio (HR) of each variable at 2, we calculated the minimal sample size at 95% confidential interval and 80% power. The minimal sample size of each group was 147 subjects. All the demographics and variables data were collected retrospectively from each patient's medical record. Primary outcome and the cases would be those who will develop in-hospital morbidity post GI, pancreatic, hepatic surgery. Controls would be those without morbidities while being admitted in the hospital post-operatively. In-hospital mortality among the groups will also be computed.

Table 1. The demographic and type of data in the study

Variable	Type of data
Gender	Categorical (male or female)
Body weight	Numerical (kilograms)
Height	Numerical (centimeters)

Table 2. The variable and type of data in the study

Variable	Type of data
Age	Numerical
Hemoglobin	Numerical
Serum albumin	Categorical
Serum sodium	Numerical
Serum creatinine	Numerical
Serum potassium	Numerical
Baseline electrocardiogram (ECG)	Categorical (normal or atrial fibrillation or any other changes)
Tumor metastasis	Categorical (primary only or nodal metastases or distant metastases)
Mode of surgery	Categorical (elective or emergency)
Blood Pressure	Categorical (SBP less than or greater than 160mmHg SBP)
Diabetes mellitus (DM)	Categorical (Presence of DM or without DM)
Morbidity	Categorical [(+) morbidity or (-) morbidity]
Mortality	Categorical [(+) mortality or (-) mortality]

Inclusion criteria are: (1) Adult patient (>18 years old); (2) Having GI, pancreatic, hepatic surgery. Exclusion criteria is incomplete medical record.

All variables of patients having in-hospital morbidity were first compared with those not having in-hospital morbidity by using univariate analysis ($\chi 2$

square test for categorical data, independent's t-test for numerical data). Crude odds ratio were estimated with their 95% confidential intervals. Variables with $p < 0.20$ in the univariate analysis were included in the multivariate analysis. We considered $p < 0.20$ in this study because the use of a more traditional level (such as 0.05) often was not able to identify some important variables. The use of higher level, in contrary, gave a possibility of including variables with questionable importance.[11,12] Logistic regression techniques were used for model development in order to obtain a specific score and an equation. Two by two analyses were used to assess interaction and confusion by fitting multiplicative models. Variables emerging with a possible prognostic value ($p < 0.20$) were entered simultaneously into multiple logistic regression models. Independent prognosis factors emerging from these logistic regression models were used to develop the scoring system to determine the best cut-off score in predicting in-hospital morbidity. Best cut-off score was determined using an ROC curve and the corresponding sensitivity and specificity at each cut-off point.

All of the variables in this study were the standard usual data in the chart. As this is a retrospective study, all information were from data written in the medical record. Only complete medical record were included in this study. Although there was a possibility of missing data bias, this study was still important as a basis to assess the risk factors significantly associated with morbidity and mortality post operatively in GI surgery patient. In order to anticipate missing data bias, all incomplete medical records were recorded separately and analyzed. The scoring system developed in this study may be externally validated with other further retrospective or prospective study.

RESULTS

A total of 285 patients were included in the study where in 143 patients had no morbidity, while 142 were considered under the group of patients who developed complications post-operatively. Moreover, among those who had morbidity, 19% of them had severe complications and eventually died. Among the 81% who were alive, most of the noted complications were acute kidney injury and hospital acquired pneumonia, which comprised 49.6% and 22.6% respectively.

Table 3. Subjects groups

Case-control group	n (%)
Normal	143
Total morbidity	142
Mortality	27 (19)
Morbidity only	115 (81)
Acute kidney injury	57 (49.6)
Hospital acquired pneumonia	26 (22.6)
Pulmonary congestion	18 (15.7)
Hypertensive crisis	8 (7.0)
Others	80 (69.6)

Univariate analysis was performed and results showed that only some of the variables below affected significantly the occurrence of morbidity. Specifically, results showed that age ($p = 0.001$), hemoglobin ($p = 0.060$), WBC ($p = 0.001$), creatinine ($p = 0.007$), serum sodium ($p = 0.018$), serum potassium ($p = 0.001$), albumin ($p < 0.001$), ECG findings ($p < 0.001$) and mode of surgery ($p < 0.001$) turned out to be significant risk factors for occurrence of morbidity. Specifically, results showed that those who were elderly (75 years old and above) had higher chances of morbidity. Similarly, those with abnormal values of Hemoglobin, WBC, serum creatinine, serum sodium, serum potassium and serum albumin were more prone to develop complications post-operatively. Furthermore, those who had ECG findings other than normal sinus rhythm were more likely to have morbidity as well. Among the subjects who developed complications post-operatively, most common ECG findings noted were ischemic changes as well as rhythm abnormalities (Table 3). Similarly, those who underwent emergency surgery had higher chances of having complications.

After considering all the risk factors that were significant in the univariate analysis, only four of them turned out to be significantly associated with increased morbidity. The results showed that those whose age was at least 75 years old was 4.06 times more likely to have morbidity as compared to those who were younger. Likewise, those with hypoalbuminemia (serum albumin ≤ 35 g/L) was 7.88 times more likely to have morbidity than those with normal albumin count. Moreover, those who had ECG findings other than normal sinus rhythm is 1.88 times more likely to have morbidity as compared to those who had normal ECG results. Lastly, those who underwent emergency surgery were 8.11 times more likely to develop complications as compared to those who had elective surgery. Among the four variables, mode of surgery was the most significant factor, followed by albumin, age and ECG result.

Table 4. Univariate analysis of risk factors

Risk factor	Without morbidity (n = 143) n (%)	With morbidity (n = 142) n (%)	p
Age			
< 75	133 (93)	112 (79)	0.0006***
≥ 75	10 (7.0)	30 (21.1)	
Gender			
Male	71 (49.7)	67 (47.2)	0.636ns
Female	72 (50.3)	75 (52.8)	
Body mass index			
(overweight and obese)	18 (12.6)	15 (10.6)	0.594ns
Hemoglobin			
Normal F: 123-153 g/L, M: 140-175 g/L	51 (36)	36 (25.3)	
Non-normal	92 (64.3)	106 (74.6)	0.0592*
White blood cell count			
Normal: 5-10 x 10^9	102 (71)	75 (52.8)	0.001***
Non-normal	41 (28.7)	67 (47.2)	
Creatinine			
Normal (F: 53-97 mmol/L)			
M: 62-115 mmol/L)	97 (68)	74 (52.1)	0.007***
Non-normal	46 (32.2)	68 (47.9)	
Sodium, Serum			
Normal: 136 – 145 mmol/L	110 (76.9)	91 (64.08)	0.018
Non-normal	33 (23.1)	51 (35.9)	
Potassium, serum			
Normal: 3.5-5.1 mmol/L	110 (76.9)	84 (59.2)	0.0013***
Non-normal	33 (23.1)	58 (40.8)	
Albumin			
Normal: 35-50 g/L	113 (79.02)	47 (33.1)	< 0.0001***
Less than 35 g/L	30 (21.0)	95 (66.9)	
Electrocardiogram			
Normal (normal sinus rhythm)	103 (78.3)	67 (57)	< 0.0001***
Non-normal	40 (21.7)	75 (43)	
ST segment depression	20	35	
T wave inversion	13	20	
Atrial fibrillation (AF) in CVR	3	8	
Atrial fibrillation (AF) in RVR	2	4	
Left ventricular hyperthrophy (LVH)	2	5	
Premature ventricular contractions (PVCs) in bigeminy	0	3	
Tumor Metastasis			
Without metastasis	76 (53)	69 (48.6)	0.443ns
With metastasis	67 (46.9)	73 (51.4)	
Diabetes melitus			
Positive	25 (17.5)	30 (21.1)	0.4426ns
Negative	118 (82.5)	112 (78.9)	
Systolic blood pressure			
>160 mmg	1 (0.7)	3 (2.1)	0.3114ns
Mode of surgery			
Emergency	5 (3.5)	38 (26.8)	0.0001***
Non-emergency	138 (96.5)	104 (73.2)	

ns:not significant; ***Significant at 1%; **5%; *10%; Chi-square test of independence was used

Table 5. Multivariate analysis

Risk factors	Without morbidity n (%)	With morbidity n (%)	Regression coefficient	SE	Odds ratio	95% CI OR	P
Age ≥ 75	10 (7.0)	30 (21.1)	1.4	0.45	4.06	1.67-9.86	0.002
Albumin (non-normal)	31 (21.7)	61 (43)	2.1	0.30	7.88	4.38-14.17	0.000
Electrocardiogram (non-normal)	40 (28.0)	75 (52.8)	0.6	0.30	1.88	1.04-3.40	0.036
Mode of surgery (emergency)	5 (3.5)	38 (26.8)	2.1	0.54	8.11	2.84-23.19	0.000

Morbidity score= (1.4 x Age ≥ 75)+(2.1 x Albumin non-normal)+(0.6 x ECG findings)+(2.1 x Emergency Surgery).

To calculate the score, the values set to each variables are as follows:

Age	Atleast 75 years old and above: 1 Below 75 year old: 0
Albumin	Normal: 0 Non-normal: 1
ECG findings	Normal sinus rhythm: 0 Finding other than NSR: 1
Mode of Surgery	Emergency: 1 Non-emergency: 0

Figure 1. The values set of each variables

The resulting p of 0.0001 suggest that the area under the curve of 0.826 was significantly different from the 0.50 area. This denotes that the new scoring system for morbidity can significantly predict the occurrence of morbidity.

Area under the curve = 0.826, p = 0.0001

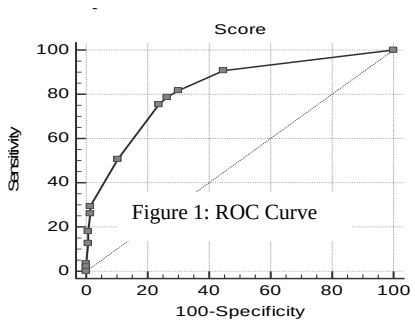


Figure 2. Receiver operating characteristic (ROC) curve

The ROC curves suggested different cut-off score. The table below reveals that the best cut-off score which gives the highest combined score of sensitivity and specificity is 1.4. Thus, those whose score is above 1.4 is expected to have morbidity. It has a sensitivity score of 78.9% and specificity of 73.4%.

DISCUSSION

This study showed that in patients who underwent GI, hepatic, pancreatic cancer surgery, age 75 years and older, abnormal albumin levels, abnormal ECG findings and the mode of surgery is associated with higher risk for complications.

As shown in previous studies, age itself is an independent risk factor in the development of complications post operatively.[13] In this study, age more than or equal to 75 years is at higher risk for morbidity representing 21% of all patients who developed complications.

Pre-operative albumin levels significantly influence the post-operative status of GI cancer patients. Low albumin levels were associated with poor wound healing, decreased collagen synthesis and impairment of immune response. All of these events lead to infections such as surgical site infections, pneumonia and anastomotic leakage.[14] In this study, abnormal values of serum albumin is also a strong predictor of morbidity among patients who underwent post GI cancer surgery (p = 0.00). Seventy percent (70%) of patients who developed complications post-operatively had lower albumin values. This study also showed that majority of the morbidities noted were due to hypoalbuminemia. These morbidities included hospital acquired pneumonia, intraabdominal infection and surgical site infections.

Abnormal ECG findings were associated with post-operative complications as stated in the study by Igari et al.[14] Similar results were noted in this study.

Table 6. Sensitivity and specificity based on cut off score

Criterion	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)	Remarks
≥0.0	100.0	0.0	49.83	-	Highest sensitivity
>0.0	90.9	55.2	66.84	85.87	
>0.6	81.7	69.9	72.96	79.37	2nd best cut-off score
>1.4	78.9	73.4	74.67	77.78	Best cut-off score
>2.0	75.4	76.2	75.89	75.69	2nd best cut-off score
>2.1	50.7	89.5	82.76	64.65	
>2.7	29.6	98.6	95.46	58.51	
>3.5	26.1	98.6	94.87	57.32	
>4.1	18.3	99.3	96.30	55.04	
>4.2	12.7	99.3	94.74	53.38	
>4.8	3.5	100.0	100.00	51.07	
>6.2	0.0	100.0	-	50.18	Highest specificity

likelihood ratio (LR) + = 2.96; LR- = 0.29

Almost 53% of patients with abrnormal ECG results developed complications after the surgery. Most of the abnormal ECG findings include rhythm abnormalities and ischemic changes. Forty nine percent of the patients who died due to complications had abnormal ECG finding, particularly ischemia.

Emergency surgery, as mentioned earlier, plays an important role in determining postoperative mortality and survival among cancer patients who undergo surgery. In a study by AL-Homoud et al, post operative mortality reaches about as high as 12% (95% CI: 10.6-13.4).[15] In this study, emergency surgery significantly predicts a higher chance of developing complications in post GI cancer patients (p = 0.000; 95% CI: 2.84-23.19).

For the RAPHA scoring system, ROC curve was plotted and it showed that the best cut-off score was 1.4. Based on this cut-off score, if the patient has fulfilled at least 1 criteria among the four variables (age ≥ 75 years old, abnormal albumin levels, abnormal ECG findings, emergency procedure), it means higher risk to develop complications post gastrointestinal, pancreatic and hepatic cancer surgery.

All data in this study was gathered retrospectively from the medical records, which is prone to recall bias and missing data bias. Another limitation of the study is that it was performed in a single center. A multicenter study is recommended for better representation of the population. Furthermore, a prospective study with a larger study population is recommended for obtaining better measure of association for some variables and validation of the scoring system.

CONCLUSION

The RAPHA scoring is a promising aid in predicting morbidity and mortality among patients who will undergo GI cancer surgery. It is important to note that this scoring system was developed to assist the internists, surgeons and anesthesiologists in evaluating the risk of these patients for complications. In a way, this tool might somehow prevent such morbidities to happen or even to lessen the rates of these complications to develop post operatively.

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