RISK FACTORS ASSOCIATED WITH IN-HOSPITAL BLEEDING COMPLICATONS IN PATIENTS UNDERGOING PANCREATICODUODENECTOMIES

by

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ABSTRACT

KEITH MURPHY. Risk factors associated with in-hospital bleeding complications in patients undergoing pancreaticoduodenectomies. (Under the direction of DR. AHMED ARIF)

Patients undergoing pancreatic surgeries have increased by over 50% in the United States over the past two decades. Pancreaticodudoenectomy, or Whipple procedure, represent a major pancreatic surgery involving surgical resection of the pancreatic head to remove cancerous tumors. This study evaluated risk factors associated with increased odds for bleeding and or hemorrhaging complications in patients who underwent pancreaticoduodenectomy. Utilizing a sample of 400 patients who underwent Whipple procedure at the Carolinas Medical Center in Charlotte, NC, a multivariate logistic regression model was generated. The model evaluated several explanatory factors including demographic, co-morbidity, medication, family history, and laboratory variables. The study identified several very significant risk factors including patient's age, race, cardiac event prior to surgery, use of loop diuretics, steroid use, family history of myocardial infarction, and serum creatinine level, with odds ratios ranging from as low as 2.82 (95% CI: 0.67, 11.97) for a family history of myocardial infarction to as high as 9.15 (95%CI: 1.89, 44.33) for a history of cardiac event. Furthermore, the model identified two factors, systolic blood pressure (adjusted OR: 0.16, 95% CI: 0.03, 0.95) and echocardiogram with stent (adjusted OR: 0.05, 95% CI: 0.003, 0.77) that were protective of bleeding or hemorrhaging complications following the Whipple procedure. In conclusion, this study identified several factors that surgeons can use to identify patients at high risk for post-surgery bleeding complications.

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INTRODUCTION

Over the past twenty years, patients undergoing pancreatic surgery procedures in the United States have increased by approximately 50% (Ziegler et al., 2010). Furthermore, patients undergoing pancreaticoduodenectomies, a surgical procedure involving resection of the pancreatic head and re-routing of the intestine to connect the remaining pancreas, stomach and gall bladder together, also increased by approximately 50% (Ziegler et al., 2010). This type of pancreatic surgery (illustrated in Figure 1) is commonly referred to as Whipple procedure.

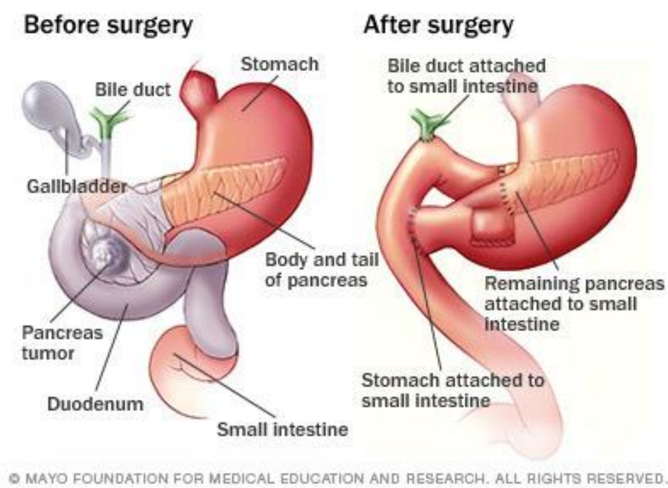

Figure 1: Anatomical description of the pylorus-preserving Whipple's procedure demonstrating surgical resection of the pancreatic head and reorganizing of the small intestine to connect the bile duct, stomach and pancreas (Mayo Clinic Foundation, 2016).

Generally, institutions performing 19 or greater Whipple procedures annually are classified as a "high-volume" center for pancreatic surgeries (Meguid, Ahuja, & Chang, 2008). Patients undergoing pancreatic surgery are at increased risk of complications such as arterial bleeding and hemorrhagic shock that could be as high as 85% (Schäfer, Heinrich, Pfammatter, & Clavien, 2011). However, early identification of bleeding or hemorrhaging is difficult due to the presence of non-specific signs and symptoms. For example, repeated gastrointestinal bleeding episodes or a decrease in serum hemoglobin can occur prior to larger bleeding episodes from other medical conditions such as pseudoaneurysms, diverticulitis, or digestive leakage (Schäfer et al., 2011).

Recently, use of predictive analytics prior to surgical procedures represents a novel method for determining patients' probability for specified complications and mortality. The American College of Surgeons-National Surgical Quality Improvement Program Database predicts patient outcomes in multiple surgical procedures including Whipple procedures. The model currently can calculate patients' probability for ten specified outcomes: chance of serious complication, any complication, death, pneumonia, urinary tract infection, renal failure, discharge to nursing or rehab facility, venous thromboembolism, cardiac complication, and surgical site infection (Parikh et al., 2010). However, the calculator does not address patient probability for in-hospital bleeding/hemorrhaging.

The division of Hepatopancreatobiliary (HPB) surgery at the Carolinas Medical Center (CMC) in Charlotte, NC, keeps a database of patients who have undergone Whipple procedure; the database currently has 400 patients who underwent the surgery from 2008-2014. This study evaluated factors associated with in-hospital bleeding/hemorrhaging complications for patients who underwent Whipple procedure at CMC Charlotte, NC using the HPB data. The results of this study will allow surgeons to identify high-risk patients and take the appropriate course of action to reduce patient risk for complications from the pancreatic surgery.

LITERATURE REVIEW

The Whipple procedure is a complex surgical procedure for removing cancerous tumors, and cysts present around the pancreatic head region (Adam et al., 2014). Previous research has reported marked decrease in post-operative mortality rates in patients undergoing Whipple procedure from 10% to approximately 5% in the United States (Adam et al., 2014; Balachandran et al., 2004). Although the post-operative mortality rates have seen marked reductions over the past two decades, the post-Whipple procedure morbidity rates remain high, ranging from a low of 20% to a high of 60% (Adam et al., 2014; Rajarathinam et al., 2008; Schäfer et al., 2011); the post-operative bleeding complications accounts for approximately 40% of all morbidity cases (Schäfer et al., 2011).

Post-operative hemorrhage, one of the more serious bleeding complications of Whipple procedure, can occur in 5-16% of patients (Balachandran et al., 2004). Post-operative bleeding is generally identified radiologically by CT scan or MRI, or surgically by bleeding from the coeliac axis, a defined area around the celiac artery in the pancreatic region (Schäfer et al., 2011). Bleeding complications could be intra-abdominal or gastrointestinal (Balachandran et al., 2004). Hemorrhage, a serious form of bleeding complication, involves acute rupturing of a blood vessel or formation of a pseudoaneurysm (Andersson, Ansari, & Andersson, 2010). Patients with hemorrhagic complications have mortality rates as high as 38% (Suzumura et al., 2014). Therefore, identifying factors that may help prevent hemorrhagic complications and post-operative bleeding has gained importance in the pancreatic surgery field.

Other studies identified several risk factors that either increase or decrease patients' probability of having in hospital bleeding/hemorrhaging complications. These factors include gender, age at the time of surgery, body mass index (BMI), diabetes status, and serum albumin levels (Balachandran et al., 2004; Cheng et al., 2005; Kanda et al., 2011; Kawai et al., 2011; La Torre et al., 2013; Matsusue, Takeda, Nakamura, Nishimura, & Koizumi, 1998)

Men undergoing pancreatic surgeries are at higher risk of bleeding complications. Balachandran et. al. conducted a retrospective analysis of 218 patients who underwent Whipple procedure between 1989-2002 at the Sanjay Gandhi Institute of Medical Sciences, India, The authors found that men have 33% increased odds of bleeding complication/hemorrhage compared to women (Balachandran et al., 2004). However, the results were not statistically significant, which may be due to a small sample size. Kawai and colleagues reported similar findings when they studied pre-operative risk factors for bleeding complications in 1,239 patients across 11 high-volume centers for pancreatic surgery in Japan; men had significantly elevated odds of in-hospital bleeding (OR=1.7, 95% CI: 1.0-3.0, $P<0.05$) as compared to women (Kawai et al., 2011). Age represents another demographic variable reported to have a significant association with post-operative bleeding complications from pancreatic surgery. Older patients aged >70 years old undergoing Whipple procedure are at higher risk of postoperative bleeding complications ($p<0.05$) as compared to patients aged <70 years old (Matsusue, Takeda, Nakamura, Nishimura, & Koizumi, 1998). Underweight patients (BMI ≤18.5) undergoing pancreatic surgery also have an increased probability for all cause morbidity complications (La Torre et al., 2013).

In addition to demographic factors, a number of studies have documented significant associations of co-morbidities and laboratory results with bleeding complications in patients undergoing pancreatic surgeries (Mansfield et al., 2006; Nakahara et al., 2012). As an example, one study concluded that a patient's American Society of Anesthesiologist's (ASA) status, a classification given by the anesthesiologist prior to surgery determining the patient's physical condition, was significantly associated with the patient requiring blood transfusion post-operatively for bleeding: when stratified for three different pancreatic surgeries, a patient of Class IV (severe systemic disease) ASA status had 24% increased risk (95% CI: 1.16-1.33, $p<0.001$) of necessitating a blood transfusion compared to patients of lower classes (Lucas et al., 2014). Other studies have documented associations between patients diagnosed with diabetes mellitus (type I and type II) and a presence of any post-operative complications, with diabetic patients having over four times the odds of a post-operative complication compared to non-diabetics (Cheng et al., 2005).

Low albumin levels during a pre-operative assessment are an indication of protein malnutrition. Low protein levels hinder clotting and coagulation which can lead to bleeding episodes (Bae et al., 2011). Patients with albumin levels of <4.0g/dl have almost twice the incidence of post-operative fistula formation compared to individuals with a pre-operative albumin level of >4.0g/dl (Kanda et al., 2011). Other researchers have noted similar associations where patients with an albumin level of <3.0 g/dl have a 25% increased risk (95% CI: 1.19-1.31, $p<0.001$) for requiring a blood transfusion for bleeding complications following the Whipple procedure (D. J. Lucas et al., 2014).

It is not uncommon to use predictive analytical models to improve the public's health status (Ingelsson et al., 2007; Szklo & Nieto, 2007). The American College of Surgeons has established a surgical risk calculator capable of predicting a patient's probability for ten specified health outcomes including chance of serious complication, any complication, death, pneumonia, urinary tract infection, renal failure, discharge to nursing or rehab facility, venous thromboembolism, cardiac complication, and surgical site infection (Bilimoria et al., 2013). Other studies have utilized predictive analytics through development of multivariate logistic regression models with the intent of predicting a particular outcome following surgery (Blackstone & Rivera, 2007; DiRusso et al., 2002; Mohiuddin et al., 2006).

Although several researchers have studied the relationship of a particular risk factor such as patient's age with in-hospital bleeding/hemorrhaging in patients undergoing Whipple procedure, no comprehensive statistical model that includes a broad spectrum of factors such as the ones included in the current study, has been developed to-date for predicting post-operative bleeding complications following the Whipple procedure.

RESEARCH QUESTION

What are the risk factors associated with in-hospital bleeding/hemorrhaging in patients who underwent Whipple procedure at the Carolinas Medical Center in Charlotte, NC from 2008 to 2014?

METHODS

Carolinas HealthCare System includes a network of 900 care locations including academic medical centers, hospitals, healthcare pavilions, physician practices, destination centers, surgical and rehabilitation centers nursing homes, hospices, and palliative care (Carolinas Healthcare System, 2016). The entire system provides care throughout North and South Carolina with an approximate ten million patient encounters annually (Carolinas Healthcare System, 2016). Furthermore, Carolinas HealthCare System delivers quality care and services to over 11,000 cancer patients annually across all care facilities in the Carolinas system. At Carolinas Medical Center (CMC) in Charlotte, NC, the hospital contributes to achieving this level of quality care among its cancer patient population. The hospital also represents a large center for clinical research with over 1100 active clinical studies at any time which synthesizes both clinical trials and NIH-supported interventional trials (Carolinas Healthcare System, 2016). In addition, the Hepatopancreatobiliary (HPB) surgery division at CMC Charlotte utilizes four specialized HPB surgeons on staff who perform over 70 Whipple surgeries annually. Over the past seven years, the department has collected data on approximately 500 patients who underwent Whipple surgery with the intent to improve current surgical outcomes and practices.

The current study used existing data collected from patients who underwent Whipple procedure at CMC from January 1, 2008 to December 31, 2014. The sample consists of 400 patients who received a pylorus-preserving or non-pylorus preserving Whipple procedure with the intent of removing any pancreatic tumor(s) located in the pancreatic head.

Power Calculation:

From the initial sample population of 400 individuals, the corresponding power calculation was determined given an increasing effect size. As mentioned in the literature review, approximately 20% (therefore the null hypothesis proportion, p0 = 0.2) of Whipple cases result in a bleeding or hemorrhaging complication postoperatively. All power analysis calculations were performed using STATA 14 statistical analysis software. For power analysis calculations, STATA utilizes the accepted default significance level (α) set at $p<0.05$. Assuming the study contains a sample size of 400 and a specified varying effect size from 0.02 to 0.1 in 0.01 unit increments, the corresponding power at each effect size increment can be determined. These results are compiled and summarized in Figure 2:

alpha	alpha_a	power	N	delta	p0	pa	diff
.05	.04547	.1542	400	.02	.2	.22	.02
.05	.04547	.2942	400	.03	.2	.23	.03
.05	.04547	.4727	400	.04	.2	.24	.04
.05	.04547	.654	400	.05	.2	.25	.05
.05	.04547	.803	400	.06	.2	.26	.06
.05	.04547	.9035	400	.07	.2	.27	.07
.05	.04547	.9594	400	.08	.2	.28	.08
.05	.04547	.9854	400	.09	.2	.29	.09
.05	.04547	.9955	400	.1	.2	.3	.1

Figure 2: Table summarizing the varying power calculations given varying effect sizes.

In addition, the change in power can also be graphed given the sample population of 400 individuals to observe the corresponding changes in power.

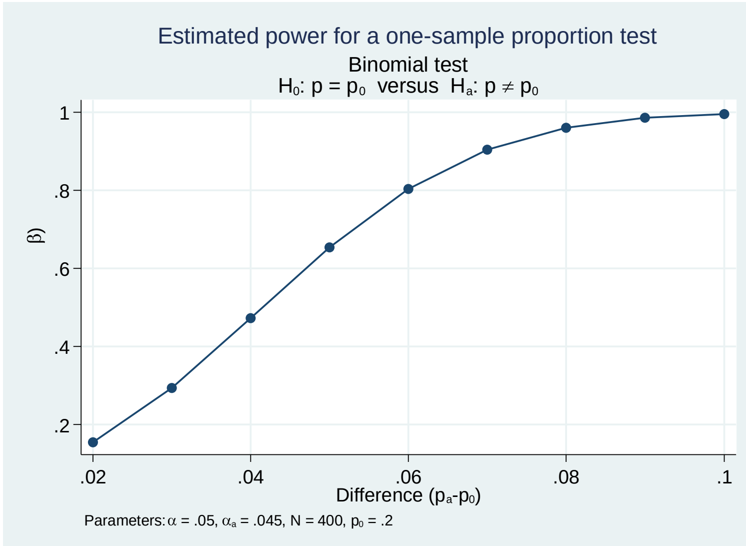

Figure 3: Stata graph outlining how power changes with increasing effect size
From the STATA output, given a sample population of 400, a p0 of 0.2, and α <0.05, an effect size of 0.06 corresponds to a power calculation of 0.8.

Measurement Variables:

The outcome variable was in-hospital bleeding/hemorrhaging, coded as 0 = patient did not have a complication involving major visceral arterial bleeding, or underwent hemorrhagic shock post-operatively while at the Carolinas Medical Center, and 1 = patient did have a complication involving major visceral arterial bleeding, or underwent hemorrhagic shock post-operatively while at the Carolinas Medical Center. The study included 44 explanatory variables: 6 demographic variables, 8 co-morbidity variables, 5 medication variables, 10 variables related to family history, and 15 laboratory variables, which were coded as continuous, categorical, or binary variables (See Appendix A). Categorical variables were coded based on the number of possibilities present in the variable, for example, patients under anesthetic receive an American Society of Anesthesiologists (ASA) class based on the patient's current physical condition (Daabiss, 2011). The variable was coded based on the five potential classifications outlined in the ASA class: Classes I-V. Where Class I identifies a completely healthy and fit patient, Class II has mild systemic disease, Class III has severe systemic disease that is not incapacitating, Class IV has an incapacitating disease that is a constant threat to life, and Class V is a moribund patient not expected to live beyond 24 hours with or without surgery (Daabiss, 2011). Finally, binary variables such as family history of cancer (all types), sex, patient smoking status, etc., were coded as binary variables. A summary of the general conceptual model for the construction of the predictive model for bleeding/hemorrhaging is included below (Figure 4):

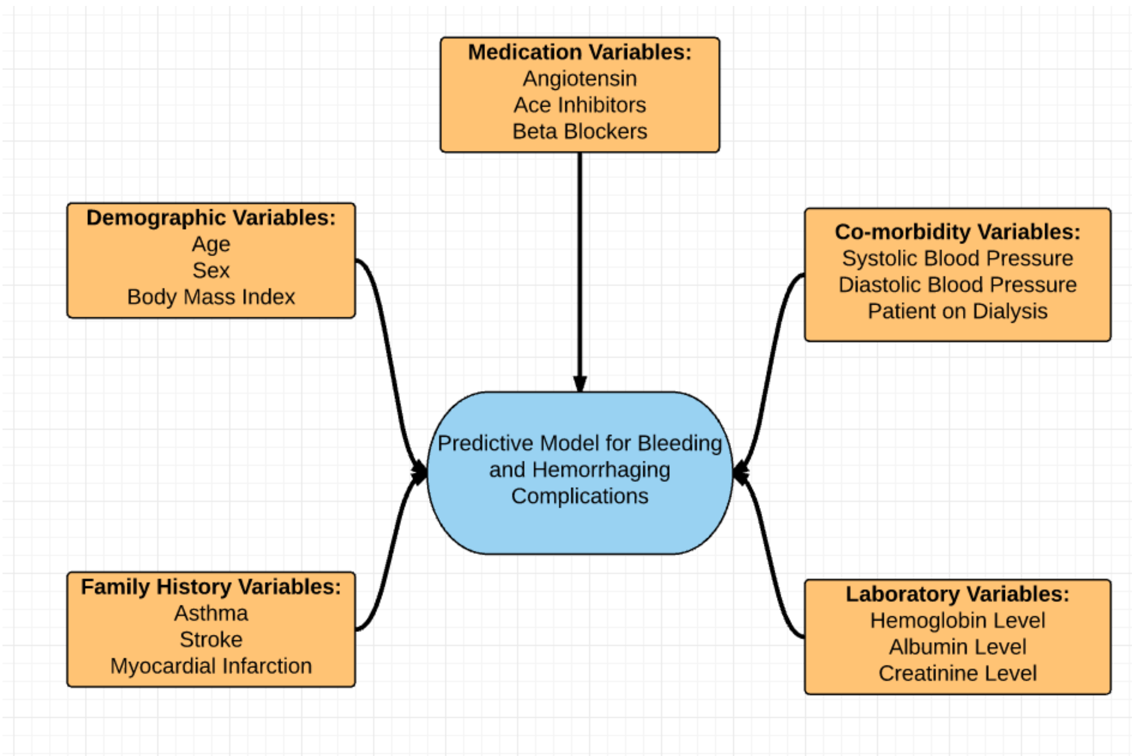

Figure 4: Conceptualized model outlining candidate variables and their potential inclusion in the predictive bleeding/hemorrhaging model.

Statistical Analysis:

To address the research question, all dependent and independent variables were first described using descriptive statistics such as sample mean or sample percentage. Following descriptive analysis of all dependent and independent variables, the 44 independent variables were evaluated for inclusion based upon clinical relevance as determined by expert opinion. Each independent variable was discussed at length with Dr. Dionisios Vrochides, Medical Research Director of the department of HPB surgery to determine, based on clinical experience, if the variable should be retained in the final model regardless of its statistical significance. All clinically relevant variables were determined before any statistical analysis was conducted. A complete list of variables is included as Appendix B. All clinical variables were included in the final model regardless of statistical significance.

Next, bivariate analysis on the remaining variables was performed using the Hosmer and Lemeshow approach (Fagerland & Hosmer, 2012). Any variable not attaining statistical significance at $p<0.25$ in the bivariate analysis was excluded from the multivariate analysis unless it was deemed clinically relevant (Table 2).

Finally, all variables significant at $p<0.25$ from the bivariate analysis as well as clinically relevant were included in the first multivariate logistic regression model.

Using the Wald test, variables not significant at $p<0.05$ were eliminated one-by-one from the multivariate model. In addition, test of collinearity was performed on variables contained in the final multivariate logistic models to ensure no collinear variables were retained in the final model. Only those variables that were statistically significant at $p<0.05$ or determined to be of clinical relevance and/or biological relevance were included in the final model (Table 3). After finalizing the predictive model for bleeding, the Hosmer and Lemeshow goodness-of fit test was performed to determine if the model was a good fit for the data. All statistical analysis was performed utilizing STATA14© Statistical Analysis Software.

Since the study utilized personal health information from patient data, all patient identification information was removed to ensure that patient privacy is kept safe. All patients received a randomly designated 'Record ID" numbered from 1-400. No identifying patient information was included in the descriptive, bivariate or multivariate analysis portion of this thesis. The study was conducted under the Carolinas Medical Center IRB sanctioned for research purposes in *Surgical Outcomes Database for Faculty of Hepatopancreatico Bilary Surgery [CHS #04-12-02E]*. This IRB authorization was in agreement with UNC Charlotte IRB.

RESULTS

Out of 400 patients who received a pylorus preserving or non-pylorus preserving Whipple procedure, 3.5% of patients had a postoperative bleeding or hemorrhaging complications. The distribution of age of patients were as follows: 53.75% of patients were <65 years old at the time of surgery, 30.25% were 65-74 years old, and 16.0% were 75 years old or older. The sample was 50% male and 77.25% of the total sample identified himself or herself as White or Caucasian. The sample population was predominantly classified as ASA class III, or having "moderate to severe systemic disease", where systemic disease includes active hepatitis, diabetes mellitus, and chronic obstructive pulmonary disease, among others (Daabiss, 2011). Further descriptive analysis showed 29.0% of the sample was current smokers, 6.8% had a previous cardiac event thirty days prior to the surgery, and 35.25% had an echocardiogram with stent placement before surgery. Over half (57.0%) of the sample population had hypertensive symptoms requiring medication. On average, patients who underwent Whipple procedure were overweight with an average body mass index (BMI) score of 26.5 (SD = 5.8). The sample population had a lower than normal hemoglobin level prior to surgery: 10.9g/dl (SD = 1.6), compared to the accepted average of roughly 14.0g/dl, suggesting the sample population was slightly anemic (Table 1).

In the univariate logistic regression analysis, 14 independent variables were identified as significant at $p<0.25$, and included in the multivariable logistic regression analysis. Three variables not meeting this inclusion criterion identified as clinically relevant (previous cardiac event 30 days prior to surgery, hypertension requiring medication, and family history of myocardial infarction) and two variables identified as biologically relevant (gender and race) were also included in the model.

. Using the Wald test criteria of $p<0.05$, each of the 19 independent variables who did not meet statistical significance were eliminated from the model unless they were determined as clinically relevant. History of severe chronic obstructive pulmonary disease ($p = 0.943$) was first eliminated from the model as it had the largest p-value. In order, family history of cancer ($p=0.772$), use of beta-blockers for treating hypertension ($p=0.551$), and steroid use for a chronic condition ($p=0.445$) were eliminated from the multivariate model. Next, tests of collinearity were performed on systolic blood pressure, family history of high blood pressure, use of loop diuretics, and hypertension requiring medication to determine any potential collinear relationships. Due to strong collinearity between loop diuretics and hypertension requiring medication (0.302, $p =<0.0001$), the latter was removed from the model. In addition, family history of high blood pressure also was removed from the model based as it was significantly correlated with the systolic blood pressure.

The final model consisted of 10 independent variables: patient age category, sex, race, systolic blood pressure, cardiac event thirty days prior to surgery, echocardiogram requiring a stent placement, hypertension medication: loop diuretic, steroid use for a chronic condition, family history of myocardial infarction, and serum creatinine levels. Despite lacking statistical significance, use of loop diuretics for hypertension, family history of myocardial infarction, and steroid use for a chronic condition were retained in the final model due to close to three-fold elevated odds ratios (2.87, 2.82, and 2.83 respectively) observed in the study.

Finally, the multivariate model was tested for fit using the Hosmer Lemeshow goodness-of-fit test. The test determined the model fits the data (p-value=0.9923).

DISCUSSION

The current study identified ten factors that were clinically, biologically, or statistically significant for determining patient probability for a bleeding or hemorrhaging complication following the Whipple surgery. These variables include age, sex, race, systolic blood pressure, cardiac event thirty days prior to surgery, echocardiogram requiring a stent placement, hypertension medication: loop diuretic, steroid use for a chronic condition, family history of myocardial infarction, and lab creatinine levels.

The current study found that patients aged 65 – 74 years have more than threefold significantly elevated odds of post-operative bleeding in the bivariate analysis. Although it became statistically non-significant after adjusting for confounders, the odds ratio remains more than threefold elevated. These results are consistent with the findings from Matsususe and colleagues who reported that patients aged 70 years or older undergoing Whipple surgery have significantly higher risk of bleeding complications as compared to patients aged <70 years old (Matsusue et al., 1998).

In the current study, non-whites were three times more likely to experience post-operative bleeding as compared to whites. Although race has not been considered a potential explanatory variable in prior studies of Whipple surgery, it is commonly included in most epidemiological studies as an important confounder (Kleinman & Norton, 2009). In other surgical procedures performed in pediatric patients, race was noted to have a significant association with mortality; black children had 1.24 times the odds (95% CI: 1.11-1.41) compared to whites children (Stone, Lapar, Kane, Rasmussen, McGahren, & Rodgers, 2013). Whether the higher odds ratio observed among non-whites in the study reflect poor baseline health such as multiple comorbidities should be analyzed in future studies.

In addition, three variables: loop diuretics, family history of myocardial infarction, and steroid use for a chronic condition were included in the final model although they did not reach statistical significance. All of these variables had almost threefold increase odds of bleeding complication following the Whipple surgery. Steroid use for a chronic condition also was observed to have a positive association in another study where authors utilizing a national database generated a multivariate risk model for 30-day mortality undergoing all-types of hepatopancreatobiliary surgery (Kneuertz et al., 2012). The authors reported almost two-fold elevated odds of 30-day mortality following postoperative hepatopancreatobiliary surgery in patients using steroids (OR: 1.80, 95% CI: 1.09-2.96) (Kneuertz et al., 2012).

Loop diuretics are commonly used in patients with symptoms of congestive heart failure. They are sometimes used to treat hypertension. This study found 2.83 times the adjusted odds (95%CI: 0.65-12.39) of post-operative bleeding in patients undergoing Whipple procedure. No prior studies in the peer-reviewed literature have evaluated the association between use of loop diuretics and in-hospital bleeding following the Whipple procedure.

The three statistically significant variables: cardiac event 30 days prior to surgery, echocardiogram with stent, and lab creatinine levels were observed to have strong associations with bleeding complication in the multivariate model. Patients with increasing levels of serum creatinine levels had 5.42 times the odds of bleeding complications. These findings are not documented in prior Whipple surgeries. However, in cardiovascular surgeries, pre-surgery increase in serum creatinine is associated with bleeding complications (Oh et al., 2011). Similarly, no prior studies were identified that compared the protective effects of placing a stent before the Whipple surgery on post-surgical bleeding complications. However, echocardiograms can provide valuable information on presence of potential embolism in arteries, which if left unchecked can cause bleeding complications (Mahmood, Christie, & Matyal, 2008). Lastly, this study identified more than nine-fold elevated odds of bleeding complications in patients who had a cardiac event prior to Whipple surgery. Although no prior studies were identified to compare these findings to, it is understandable that patients with recent cardiac event could be at-risk of post-operative complications.

Limitations:

One limitation acknowledged in undertaking this study involves the hospital characteristics at CMC-Charlotte. Due to high volume of pancreatic surgeries performed in the Hepatopancreatobiliary department, patient demographics, particularly race and ethnicity, can predict the type of center a patient will travel to with the intent of receiving care (Liu et al., 2006). In addition, high volume centers also have lower overall rates for morbidity complications and mortality as compared to low-volume and intermediate volume centers for pancreatic surgery (Amini, Spolverato, Kim, & Pawlik, 2015). Consequently, although the multivariate model may be capable of predicting patient probability for post-operative in-hospital bleeding/hemorrhaging at CMC, a high volume center for pancreatic surgeries, the model may not be applicable to other hospital systems with an intermediate or low volume of pancreatic surgeries.

Another potential study limitation involves the medical record data obtained as part of the study. As clinical information systems continue to improve, the level of accuracy and quantity of information may not have improved concurrently, which has been especially prevalent in the last decade (Berkowitz & McCarthy, 2013). Therefore, the records taken from early 2008-2009 may not have the same quality of information available as those taken more recently in 2013-2014 from the Hepatopancreatobiliary medical records database.

Some variables, especially the laboratory variables, had a high frequency of missing data. For example, the lipase laboratory variable had only 124 observations. Due to such a low number of observations and to avoid list-wise deletion, these variables were not considered for inclusion in the multivariate analysis. In addition, other independent variables, e.g., family history of asthma, were excluded from multivariate analysis due to too few individuals with the outcome.

One final limitation that can arise from this study involves the potential for absence of other potential confounders in the final predictive model. For example, one study investigating the predictive accuracy of models involving lung cancer acknowledged investigating only twelve variables when past research suggests that over 100 variables may accurately predict the outcome (Bartfay, Mackillop, & Pater, 2006). Based on feasibility and timeline issues, this current study included all relevant variables in the model available based on the information offered from the Hepatopancreatobiliary department. However, other potential significant variables might exist beyond the variables present in the database.

Although the multivariate model has been generated, in order to validate the model to test its predictive accuracy, the study necessitates a validation dataset where the patient's characteristics can be entered into the predictive model and the corresponding probabilities can be recorded for analysis (Cawley & Talbot, 2006). In addition, the receiver operating characteristic (ROC) area analysis can be used to measure the model's ability to correctly classify those with or without the specified outcome. By utilizing the validation dataset and the corresponding ROC value, the predictive model generated from the study can be assessed to determine its predictive accuracy in determining a patient's probability for a bleeding and/or hemorrhaging complication.

Although hospital mortality rates have decreased in patients undergoing Whipple procedure in the past decade, the mortality rates remain high in patients who experience an in-hospital bleeding/hemorrhaging complication following the surgery (Suzumura et al., 2014). Results from this study can be used by surgeons to target patients at high risk for bleeding complications and take appropriate steps minimize post-operative complications.

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TABLES

Table 1: Descriptive analysis of bleeding/hemorrhaging variable and all socio-demographic, co-morbidity, medication, family history and laboratory variables*

Variables	**N**	**% or Mean (SD)**
Socio-demographic		
Patient Age Category		
<65 years old	215	53.75
65-74 years old	121	30.25
75+ years old	64	16.0
Sex		
Female	200	50.0
Male	200	50.0
Race		
White/Caucasian	309	77.25
Black/AA	80	20.0
Asian	2	0.5
Unknown	9	2.25
Current Smoker		
No	276	69.0
Yes	118	29.0
Current alcohol usage		
No	225	56.3
Yes	166	41.5
Body Mass Index (kg/m)		
Normal (BMI <25)	173	43.1
Overweight (b/w 25 and 30)	130	32.4
Obese (BMI≥30)	96	23.9
Comorbidities		
Diabetes requiring medication		
None	277	69.3
Oral Medication	69	17.3
Insulin Medication	49	12.3
Hypertension requiring medication		
No	168	42.0
Yes	228	57.0
Systolic blood pressure		
<140 mmHg	251	62.6
≥140 mmHg	133	33.2
Diastolic blood pressure		
< 90 mmHg	341	85.0
≥90 mmHg	43	10.7
Previous cardiac event within thirty day prior to surgery		

Variables	N	% or Mean (SD)
No	368	92.0
Yes	27	6.8
Echocardiogram with stent placement before surgery		
No	259	64.75
Yes	141	35.25
History of severe chronic obstructive pulmonary disease		
No	380	95.0
Yes	16	4.0
Patient is on dialysis		
No	369	92.3
Yes	5	1.3
Medications		
Hypertension medication: angiotensin		
No	303	75.75
Yes	97	24.25
Hypertension medication calcium blockers		
No	364	91.0
Yes	36	9.0
Hypertension medication: ace inhibitors		
No	326	81.5
Yes	74	18.5
Hypertension medication: loop diuretics		
No	340	85.0
Yes	60	15.0
Hypertension medication : beta blockers		
No	381	95.25
Yes	19	4.75
Steroid use for a chronic condition		
No	371	92.8
Yes	22	5.5
Family History		
Family history of Asthma		
No	398	99.5
Yes	2	0.5
Family history of Cancer		
No	222	55.5

Variables	**N**	**% or Mean (SD)**
Yes	178	44.5
Family History of Deep Vein Thrombosis		
No	399	90.75
Yes	1	0.25
Family history of Diabetes		
No	284	71.0
Yes	116	29.0
Family history of myocardial infarction		
No	353	88.25
Yes	47	11.75
Family history of high blood pressure		
No	280	70.0
Yes	120	30.0
Family history of high cholesterol		
No	391	97.25
Yes	9	2.25
Family history of sleep apnea		
No	400	100.0
Yes	0	0
Family history of stroke		
No	373	93.25
Yes	27	6.75
Family history of hepatopancreatobiliary disease		
No	384	96.0
Yes	16	4.0
Laboratory variables		
Lab hemoglobin level	400	10.9 (1.6)
Lab platelet level	400	220.9 (84.3)
Lab partial thromboplastin time	291	30.2 (11.0)
Lab alkaline phsophatase level	375	202.7 (218)
Lab Amylase level	69	89.0 (83.5)
Lab aspartate aminotrasferase level	371	82.1 (86.4)
Lab direct bilirubin level	168	3.7 (18.4)
Lab lipase level	124	70.9 (106.2)
Lab Serum Alpha-Fetoprotein level	143	3.7 (2.6)
Lab carcinoembryonic antigen level	164	13.1 (64.9)
Lab Ca-19-9 level	262	522.5 (2093.2)
Lab Potassium level	399	4.2 (0.6)
Lab creatinine level	400	0.9 (0.3)
Albumin level	382	3.4 (0.7)

Variables	**N**	**% or Mean (SD)**
Bleeding Complication		
No	386	96.5
Yes	14	3.5
American Society of Anesthesiologists Classification		
Class II	50	12.5
Class III	313	78.3
Class IV	33	8.3

n may not sum to 100% due to missing values

Table 2**:** Bivariate association between "Bleeding" variable and all independent variables

Variables	**% Bleeding**	**Unadjusted OR**	**95% CI**	**p-value for χ^2**
Socio-demographic				
Patient Age Category				
<65 years old	1.9	1.0		0.074
65-74 years old	6.6	3.73	(1.10, 12.67)	
75+ years old	3.1	1.70	(0.30, 9.51)	
Sex				
Female	2.5	1.0		0.276
Male	4.5	1.83	(0.60, 5.58)	
Race				
White/Caucasian	3.2	1.0		0.584
Non-White	4.4	1.39	(0.43, 4.54)	
Current Smoker				
No	4.0	1.0		0.478
Yes	2.5	0.63	(0.17, 2.30)	
Current alcohol usage				
No	3.6	1.0		0.982
Yes	3.6	1.01	(0.34, 2.98)	
Body Mass Index (kg/m)				
Normal (BMI <25)	3.5	1.0		0.907
Overweight (b/w 25 and 30)	3.1	0.88	(0.24, 3.20)	
Obese (BMI≥30)	4.2	1.21	(0.33, 4.40)	
Comorbidities				
Diabetes requiring medication				
None	3.3	1.0		0.492
Oral Medication	5.8	1.83	(0.55, 6.14)	
Insulin Medication	2.0	0.62	(0.08, 5.01)	
Hypertension requiring medication				
No	1.2	1.0		0.047
Yes	5.3	4.61	(1.02, 20.88)	
Systolic blood pressure				
<140 mmHg	4.8	1.0		0.103
≥140 mmHg	1.5	0.30	(0.07, 1.38)	
Diastolic blood pressure				
< 90 mmHg	3.52	1.0		0.709
≥90 mmHg	4.65	1.34	(0.29, 6.19)	

Variables	% Bleeding	Unadjusted OR	95% CI	p-value for χ^2
Previous cardiac event within thirty day prior to surgery				
No	2.7	1.0		0.001
Yes	14.8	6.23	(1.81, 21.38)	
Echocardiogram with stent placement before surgery				
No	5.0	1.0		0.025
Yes	0.7	0.14	(0.02, 1.04)	
History of severe chronic obstructive pulmonary disease				
No	3.2	1.0		0.047
Yes	12.5	4.38	(0.89, 21.47)	
Patient is on dialysis				
No	3.8	1.0		0.657
Yes	0.0	1	--	
Medications				
Hypertension medication: angiotensin				
No	3.0	1.0		0.308
Yes	5.2	1.78	(0.58, 5.43)	
Hypertension medication calcium blockers				
No	3.6	1.0		0.805
Yes	2.8	0.77	(0.01, 6.07)	
Hypertension medication: ace inhibitors				
No	3.1	1.0		0.323
Yes	5.4	1.81	(0.55, 5.92)	
Hypertension medication: loop diuretics				
No	2.9	1.0		0.148
Yes	6.8	2.36	(0.71, 7.78)	
Hypertension medication: beta blockers				
No	3.2	1.0		0.088
Yes	10.5	3.6	(0.75, 17.46)	
Steroid use for a chronic condition				

Variables	**% Bleeding**	**Unadjusted OR**	**95% CI**	**p-value for χ^2**
No	3.2	1.0		0.150
Yes	9.1	2.99	(0.63, 14.28)	
Family History				
Family history of Asthma				
No	3.5	1.0		0.787
Yes	0.0	1	--	
Family history of Cancer				
No	4.5	1.0		0.222
Yes	2.3	0.5	(0.15, 1.58)	
Family History of Deep Vein Thrombosis				
No	3.5	1.0		0.849
Yes	0.0	1	--	
Family history of Diabetes				
No	3.9	1.0		0.525
Yes	2.6	0.66	(0.18, 2.41)	
Family history of myocardial infarction				
No	2.8	1.0		0.047
Yes	8.5	3.19	(0.96, 10.62)	
Family history of high blood pressure				
No	4.6	1.0		0.057
Yes	0.8	0.17	(0.02, 1.33)	
Family history of high cholesterol				
No	3.6	1.0		0.563
Yes	0.0	1	--	
Family history of sleep apnea				
No	3.5	1.0		--
Yes	0.0	1	--	
Family history of stroke				
No	3.8	1.0		0.305
Yes	0.0	1	--	
Family history of hepatopancreatobiliary disease				
No	3.65	1.0		0.437
Yes	0.0	1	--	
Laboratory variables				

Variables	% Bleeding	Unadjusted OR	95% CI	p-value for χ^2
Lab hemoglobin level		0.90	(0.65, 1.26)	0.555
Lab platelet level		1.00	(0.99, 1.00)	0.439
Lab partial thromboplastin time		1.00	(0.95, 1.05)	0.972
Lab alkaline phsophatase level		1.00	(1.00, 1.00)	0.705
Lab Amylase level		0.97	(0.90, 1.05)	0.486
Lab aspartate aminotrasferase level		0.99	(0.98, 1.00)	0.155
Lab direct bilirubin level		1.00	(0.94, 1.07)	0.978
Lab lipase level		1.01	(1.00. 1.03)	0.081
Lab Serum Alpha-Fetoprotein level		0.83	(0.23, 3.10)	0.791
Lab carcinoembryonic antigen level		1.00	(0.98, 1.02)	0.924
Lab Ca-19-9 level		1.00	(1.00, 1.00)	0.909
Lab Potassium level		1.21	(0.49, 2.99)	0.673
Lab creatinine level		2.66	(1.07, 6.62)	0.035
Albumin level		0.78	(0.36, 1.67)	0.518
American Society of Anesthesiologists Classification				
Class II	0.0	1.0		0.000
Class III	1.9	0.06	(0.02, 0.19)	
Class IV	24.2	1	--	

Table 3: Final Multivariate Logistic Regression Model between “Bleeding” Variable and all Clinical, Statistical, and. Biologically Relevant Independent Variables

Variables	Adjusted OR	95% CI	p-value
Socio-demographic			
Patient Age Category			
<65 years old	1.0		
65-74 years old	3.18	(0.76, 12.43)	0.114
75+ years old	0.78	(0.09, 6.34)	0.813
Sex			
Female	1.0		
Male	0.91	(0.24, 3.46)	0.891
Race			
White/Caucasian	1.0		
Non-White	2.99	(0.72, 12.34)	0.130
Comorbidities			
Systolic blood pressure			
<140 mmHg	1.0		
≥140 mmHg	0.16	(0.03, 0.95)	0.044
Previous cardiac event within thirty days prior to surgery			
No	1.0		
Yes	9.15	(1.89, 44.32)	0.006
Echocardiogram with stent placement before surgery			
No	1.0		
Yes	0.14	(0.002, 0.77)	0.032
Steroid Use for A Chronic Condition			
No	1.0		
Yes	2.87	(0.42, 19.52)	0.281
Medications			
Hypertension medication: Loop Diuretics			
No	1.0		
Yes	2.83	(0.65, 12.39)	0.167
Family history of Myocardial Infarction			
No	1.0		
Yes	2.82	(0.66, 11.97)	0.159
Laboratory Variables			
Lab creatinine level	5.42	(1.39, 21.17)	0.035

APPENDIX A: DATA CODING

Appendix A**:** Description of all variables, STATA coding name, and coding designation

Description	**Variable Name**	**Coding**
Age Group	Agegroup	0 = <65yrs old 1 = 65-74yrs old 2 = 75+ yrs old
Sex	Sex	0 = female 1 = male
ASA Class	ASA	0= Class II 1 = Class III 2= Class IV
Steroid (Use for a chronic condition)	steroid	0 = No 1 = Yes
Diabetes (requiring medication)	diabetes	0 = No 1 = Oral Medication 2 = Insulin Dependent
Hypertension (requiring medication)	hypertension	0 = No 1 = Yes
Current Smoking Status	smoker	0 = No 1 = Yes
History of Severe COPD	COPD	0 = No 1 = Yes
Dialysis	dialysis	0 = No 1 = Yes
American Indian or Alaska Native	AmIndorAlaska	0 = No 1 = Yes
Asian	Asian	0 = No 1 = Yes
Black or African American	BlackorAA	0 = No 1 = Yes
Native Hawaiian	hawaii	0 = No 1 = Yes
White or Caucasian	white	0 = No 1 = Yes
Other Race	other	0 = No 1 = Yes
Family history of diabetes	famhistdiabetes	0 = No 1 = Yes
Family history of Myocardial Infarction	famhistMI	0 = No 1 = Yes
Family history of high cholesterol	Famhistchol	0 = No 1 = Yes
Family history of sleep apnea	famhistsleep	0 = No

		1 = Yes
Family history of stroke	Famhiststroke	0 = No 1 = Yes
Family history of HBP disease	famhistHBP	0 = No 1 = Yes
Hypertension Medication: Angiotensin	Hypmed1	0 = No 1 = Yes
Hypertension Medication: Calcium Channel Blockers	Hypmed2	0 = No 1 = Yes
Hypertension Medication: Ace Inhibitors	Hypmed3	0 = No 1 = Yes
Hypertension Medication: Loop diuretics	Hypmed4	0 = No 1 = Yes
Hypertension Medication: Beta Blockers	Hypmed5	0 = No 1 = Yes

Description	**Variable Name**	**Units**
Lab hemoglobin level	Lab_hgb	g/dl
Lab platelet level	Lab_plt	K/uL
Lab partial thromboplastin time	Lab_ptt	Seconds
Lab alkaline phsophatase level	Lab_alkp	IU/L
Lab Amylase level	Lab_amy	U/L
Lab aspartate aminotrasferase level	Lab_ast	IU/L
Lab direct bilirubin level	Lab_directbil	mg/dl
Lab lipase level	Lab_lip	U/L
Lab Serum Alpha-Fetoprotein level	Lab_afp	ng/ml
Lab carcinoembryonic antigen level	Lab_cea	ng/ml
Lab Ca-19-9 level	Lab_ca199	U/ml
Lab Potassium level	Lab_k	Mmol/L
Lab creatinine level	Lab_creat	mg/dl
Albumin level	Albumin	g/dl
Medical weight	med_his_weight	lbs
Medical History weight (6 months before surgery)	med_his_weight_6mo	lbs
BMI	BMI	Not applicable
Systolic Blood Pressure	bp_sys	mmHg
Diastolic Blood Pressure	bp_dias	mmHg
Height	Height	Inches
Weight	Weight	lbs

APPENDIX B: CLINICAL REASONING

Appendix B: Clinically relevant variables utilized in prediction modeling.

Clinically Relevant Variables	Reasoning
Patient Age Category	Generalized demographic
Race	Generalized demographic
Sex	Generalized demographic
Previous cardiac event thirty days prior to surgery	Those patients with cardiac events were observed to have higher rates of bleeding
Lab hemoglobin level	Low hemoglobin levels generally associated with less likelihood for clotting
Hypertension requiring medication	High blood pressure in patients had significant associations with bleeding due to lack of clotting.
Family history of Myocardial Infarction	Pattern of MI observed among patients who had a bleeding complication.