Impact of Diabetes on Postoperative Outcomes Following Colon Cancer Surgery

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BACKGROUND: Diabetes is the sixth most common cause of death in the US and causes significant postoperative mortality and morbidity.

OBJECTIVE: To characterize the impact of diabetes among patients undergoing surgery for colorectal cancer.

DESIGN: This is is a retrospective cohort study.

PARTICIPANTS: Patients in the Nationwide Inpatient Sample (NIS) who had undergone colorectal cancer surgery between 1998 and 2005.

MEASUREMENTS: Using multivariate regression, we determined the association of diabetes status with postoperative mortality, postoperative complications, and length of stay.

KEY RESULTS: An estimated 218,534 patients had undergone surgery for colorectal cancer. We categorized subjects by the presence of diabetes, the prevalence of which was 15%. Crude postoperative in-hospital mortality was lower among diabetics compared to non-diabetics (2.5% *vs.* 3.2%, $P<0.0001$). Adjusted mortality was 23% lower in those with diabetes compared to non-diabetics (aOR 0.77; 95% CI: 0.71–0.84). Diabetics also had lower adjusted post-operative complications compared to non-diabetics (aOR 0.82; 95% CI: 0.79–0.84). In uninsured individuals and patients <50 years of age, there was no protective association between diabetes and either in-hospital mortality or postoperative complications.

CONCLUSIONS: In patients undergoing colorectal cancer surgery, those with diabetes had a 23% lower mortality and fewer postoperative complications compared to non-diabetics. The mechanisms underlying this unexpected observation warrant further investigation.

KEY WORDS: diabetes; nationwide; colorectal cancer; hyperglycemia.
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INTRODUCTION

Diabetes affects 7% of the US population[1] and is the sixth most common cause of death in the US. Diabetics have a 50% chance of requiring surgery at some point in their lives,[2] and the proportion of surgical patients with diabetes is close to 20%.[3] Diabetic patients often have microvascular and marcrovascular pathology[4] that influences their perioperative course[5] and have a significantly higher risk of perioperative infection and post operative cardiovascular morbidity and mortality.[6-9]

Hyperglycemia may be the underlying factor that mediates worse outcomes in diabetics. The association between hyperglycemia and infection has been long recognized; studies report diverse defects in neutrophil and monocyte dysfunction such as adherence, chemotaxis and phagocytosis,[10,11] while improvement in blood sugars helps restore granulocyte function.[12] Additionally, acute hyperglycemia may impair the protective effects of cardiac ischemic preconditioning which may lead to more extensive myocardial injury.[13] As well, hyperglycemia appears to increase inflammatory markers and oxidative stress resulting in endothelial cell dysfunction and therefore promoting thrombosis.[3]

Diabetes may have a particularly negative impact on individuals undergoing colorectal cancer surgery because of the patients' older age and the procedure's inherent higher risk. We have conducted this administrative claims study to explore and generate further hypotheses regarding the potential impact of diabetes on mortality following colorectal surgery for cancer, we conducted a nationwide, population-based analysis using the Nationwide Inpatient Sample. We further sought to distinguish whether the presence of the long-term complications of diabetes further accentuated the disease's impact on post-surgical outcomes relative to uncomplicated diabetes and no diabetes.

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METHODS

Data Source

All data were extracted from the Nationwide Inpatient Sample (NIS) between 1998 and 2005. The NIS is the largest all-payer database of national hospital discharges, maintained as part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ). The NIS is a 20% stratified sample of non-federal, acute-care hospitals in the United States. Each record in the NIS includes a unique identifier, demographic data (age, gender, and race), hospital transfer status, admission type (emergent, urgent, or elective), primary and secondary diagnoses (up to 15), primary and

secondary procedures (up to 15), expected primary and secondary insurance payers, total hospital charges, length of stay, and hospital characteristics (region, urban versus rural location, bedsize, teaching status). The NIS data concur with the National Hospital Discharge Survey, supporting data reliability[14].

We used Clinical Modification of the International Classification of Diseases, 9th Revision (ICD-9-CM) procedural codes to identify all patients in the NIS between 1998 and 2005 who met the following criteria: (i) had a diagnosis of colorectal cancer (ICD-9-CM codes: 153.0–154.8, 209.10–209.17, 230.3–230.6, 796.70–796.76, V10.05–V10.06); and (ii) who had undergone partial colectomy (45.71–45.79), total colectomy (45.8), or proctectomy (48.41–48.49, 48.5, 48.63–48.69) as identified by ICD-9-CM procedural codes.

Predictor and Outcome Variables

ICD-9-CM diagnostic codes were used to identify patients with uncomplicated diabetes (250.0-250.3, 250.8, 250.9) and diabetes with complications (250.4–250.7), which included renal, ophthalmological, neurological, or peripheral vascular manifestations. Case-mix adjustment was performed using 17 individual comorbidity conditions that are components of the validated Charlson Index.[15] We modified the Charlson Index to exclude diabetes as it was our main predictor of interest. In-hospital mortality was the primary outcome. Secondary outcomes included measures of post-operative complications and length of stay. We used ICD-9-CM coding algorithms to identify postoperative complications which were then further categorized as wound infections, urinary, gastrointestinal (including acute liver injury), pulmonary, cardiac, and intra-operative complications.

Statistical Analysis

Data were analyzed using the Stata 10.0 SE software package (Stata Corp LP, College Station, Texas). All analyses were stratified by the presence of no diabetes, uncomplicated diabetes, and complicated diabetes. These analyses took into account the stratified two-stage cluster design using Stata's SVY (survey data) commands incorporating individual discharge-level weights. Two-way χ^2 analyses and the Fischer's exact test were performed to compare categorical variables among different subgroups while unpaired t-tests compared differences in means of continuous variables. Multivariate logistic regression analysis was used to determine the association between mortality and the presence of uncomplicated and complicated diabetes, age, gender, primary health insurance carrier, non-diabetic comorbidities, type of admission (elective vs. non-elective), median neighborhood income, and teaching vs. non-teaching hospital status. We performed a subgroup analysis of only individuals younger than 50 years of age. We used similar multivariate logistic and linear regression models to determine the association between diabetes status and postoperative complications and length of stay, respectively.

Ethical Considerations

The analysis of the Nationwide Inpatient Sample uses completely unidentified data with no risk of loss of confidentiality. An initial expedited review by the Institutional Review Board of the Johns Hopkins Medical Institutions deemed this study exempt from further ethical review.

RESULTS

Baseline Demographic and Clinical Characteristics

There were 218,534 patients who underwent surgery for colorectal cancer between 1998 and 2005. Eighty five percent of this population was non-diabetic, and the remainder (15%) diabetic. The prevalence of uncomplicated and complicated diabetes was 14% and 1%, respectively. Patients with diabetes were older, more likely to be male and more likely to earn below the national median than non-diabetics. The type of health insurance did not differ among the four groups (Table 1).

Preoperative comorbidities are shown in Table 1. Patients with diabetes, both complicated and uncomplicated, had a higher rate of ischemic heart disease, heart failure, renal failure and cerebrovascular disease compared to non-diabetics. All comorbid conditions occurred more frequently in the complicated diabetes group compared to the uncomplicated diabetic group.

In-Hospital Mortality

Crude postoperative in-hospital mortality was 3.2% in those without diabetes versus 2.5% in those with diabetes. After adjustment for confounders, adjusted mortality was 23% lower in those with diabetes compared to non-diabetics (aOR 0.77; 95% CI: 0.71–0.84), and this association did not differ for elective vs. non–elective admissions.

When we stratified diabetic patients by the presence of diabetic complications, the in-hospital mortality was 2.4% in the uncomplicated diabetes group compared with 4.2% in the complicated diabetes group. The adjusted mortality for uncomplicated diabetics was lower than that of non-diabetics among both elective (aOR 0.71; 95% CI: 0.61-0.83) and non-elective (aOR 0.75; 95% CI: 0.67–0.83) admissions. However, among complicated diabetics, in-hospital mortality was two-fold higher for elective admissions relative to non-diabetics (aOR 2.14; 95% CI: 1.55–2.98). For non-elective admissions, there was no difference in in-hospital mortality between non-diabetics and those with complicated diabetes (aOR 0.91; 95% CI: 0.67-1.23).

Postoperative Complications

The occurrence of any postoperative complication was lower among diabetics compared to non-diabetics (28% vs. 31%, $P< 0.0001$). Rates of mechanical and infectious wounds, urinary, pulmonary, gastrointestinal, and intraoperative complications were lower in diabetics than in non-diabetics (Table 2). After multivariate adjustment for confounders, diabetics had lower odds of having at least one postoperative complication com-

Table 1. Baseline Demographics and Comorbidity

	Non-diabetics (N=184,951)	Diabetics		
		All Diabetics (N=33,583)	Uncomplicated Diabetes (N=31,313)	Complicated Diabetes (N=2,270)
Mean age (yr) (SD)	69.0 (13.4)	70.7 (10.5)[a]	70.7 (10.6)[a]	70.2 (10.0)[a]
Female (%)	51.0%	47.6%[a]	47.6%[a]	46.7%[a]
Median income > National median	63.9%	59.7%[a]	59.5%[a]	62.9%
Teaching hospital	42.9%	42.3%[a]	42.3%	43.0%
Health insurance				
Private	32.2%	24.7%	25.1%	19.9%
Medicare	60.9%	68.8%	68.4%	74.1%
Medicaid	3.4%	3.7%	3.7%	3.9%
Self-pay	1.9%	1.5%	1.5%	0.7%
Other	1.6%	1.3%	1.3%	1.4%
Charlson Index (SD)	4.7 (3.1)	5.7 (3.0)[a]	5.6 (3.0)[a]	7.0 (3.0)[a]
Specific comorbid conditions				
Ischemic heart disease	4.2%	7.0%[a]	6.9%[a]	8.2%[a]
Congestive heart failure	8.6%	13.8%[a]	13.0%[a]	24.5%[a]
Pulmonary disease	14.0%	13.9%	14.0%	13.2%
Cerebrovascular disease	2.1%	3.3%[a]	3.3%[a]	4.2%[a]
Renal failure	1.4%	3.5%[a]	2.0%[a]	23.2%[a]
Hemiplegia	0.3%	0.3%	0.3%	0.3%

[a]*Statistically significant*

pared to non-diabetics (aOR 0.82; 95% CI: 0.79–0.84). In secondary analysis that stratified complicated vs. uncomplicated diabetes, there was a difference in the rate of any postoperative complication between uncomplicated diabetes and non-diabetics (28% *vs.* 31%, respectively, P<0.0001), while complicated diabetics complicated diabetes had modestly higher rates of any postoperative complication compared to non-diabetics (33.5% vs. 31.2%, P=0.02). Additionally, uncomplicated diabetic subjects had a lower rate of wound, urinary, pulmonary and gastrointestinal complications compared to non-diabetics. In contrast, patients with complicated diabetes had higher urinary, pulmonary, gastrointestinal and cardiac complications than non-diabetics (Table 2). After controlling for age, sex, elective admission status, comorbidity, teaching hospital status, and median neighbourhood income, those with uncomplicated diabetes had lower adjusted post-operative complications compared to non-diabetics (aOR 0.80; 95% CI: 0.78–0.83), while subjects with complicated diabetes did not differ from the latter with respect to any post-operative complication (aOR 1.00; 95% CI: 0.91–1.16).

Subgroup Analyses

To address whether the mortality benefit associated with uncomplicated diabetes may have been partly due to unrecognized comorbidity in the reference non-diabetic population, we conducted a subgroup analysis of individuals younger than 50 years, who are less likely to have comorbid conditions than older patients. Patients who had uncomplicated diabetes but were under the age of 50 years had no difference in in-hospital mortality compared to non-diabetic counterparts after multivariate adjustment (aOR 1.07; 95% CI: 0.43–2.69). With respect to postoperative complications, patients with uncomplicated diabetes who were under 50 years had similar likelihood of postoperative complications as non-diabetics (aOR 1.02; 95% CI: 0.86–1.21).

Table 2. Postoperative Complications

	Non-diabetics (N=184,951)	Diabetics		
		All Diabetics (N=33,583)	Uncomplicated Diabetes (N=31,313)	Complicated Diabetes (N=2,270)
Any postoperative complication	31.2%	27.9%[a]	27.5%[a]	33.5%
Mechanical wound	1.3%	1.0%[a]	1.1%[a]	1.0%
Infectious wound	5.6%	4.3%[a]	4.2%[a]	5.9%
Urinary	1.7%	1.6%[a]	1.5%[a]	2.8%[a]
Pulmonary	7.7%	6.5%[a]	6.2%[a]	10.8%[a]
Gastrointestinal	16.4%	13.2%[a]	13.2%[a]	13.8%[a]
Cardiac	5.1%	5.1%	5.0%	6.4%[a]
Intraoperative complication	3.4%	2.7%[a]	2.7%[a]	3.1%

[a]*Statistically significant*

To explore this possibility that diabetics may be more likely referred to pre-operative internal medicine or anaesthesia clinics and allowing for enhanced medical optimization and post-operative follow-up, we conducted subgroup analysis with uninsured patients who would be assumed to have less access to peri-operative care. The reduced in-hospital mortality observed in uncomplicated diabetics was absent among the subgroup that was uninsured (aOR 0.99; 95% CI: 0.39–2.52). Similarly, among uninsured patients, the likelihood of postoperative complications was similar between non-diabetics and those with uncomplicated diabetes (aOR 1.09; 95% CI: 0.86–1.39).

Hospital Utilization

The average hospital length of stay was 9.9 days in both diabetics and non-diabetics. However, after stratification for diabetic complications, length of stay was modestly shorter in uncomplicated diabetics compared to non-diabetics (9.7 vs. 9.9 days, P<0.01) while it was longer in complicated diabetics than in either non-diabetics or uncomplicated diabetics (12.6 vs. 9.9 and 9.7 days, respectively, P<0.01). Compared to non-diabetics, adjusted length of stay was 2% shorter for uncomplicated diabetics and 16% longer for complicated diabetics after controlling for elective admission status, age, sex, comorbidity, health insurance payer, teaching hospital status, and median income.

DISCUSSION

Previous studies have shown that diabetics have a higher risk of postoperative complications and mortality.[6-9] In our nationwide analysis of over two hundred thousand patients who underwent surgery for colorectal cancer, patients with diabetes had a lower mortality than those without diabetes. Ninety three percent of the diabetic population had uncomplicated diabetes. Patients with uncomplicated diabetes had up to a 25% reduction in adjusted mortality compared to those without diabetes. Uncomplicated diabetics also had fewer postoperative complications compared to non-diabetics. This protective effect was not apparent in patients with complicated diabetes.

There are several factors that may contribute to our unexpected findings. Firstly, we would expect that uncomplicated diabetics as a group were more likely to have adequate glycemic control than those with complicated diabetes. Randomized trials have demonstrated that in the critically ill, aggressively trying to achieve normoglycemia does not appear to confer any added benefit compared to less intensive glycemic control, and may in fact cause greater harm[15] Thus, mild hyperglycemia does not seem to lead to increased inpatient complications. Possibly, uncomplicated diabetics are less likely to sustain the more extreme levels of hyperglycemia necessary to cause significant peri-operative morbidity.

However, this hypothesis does not account for why uncomplicated diabetics would have an improved outcome compared to non-diabetics. We conjecture that patients with diabetes may receive better peri-operative medical care than non-diabetics. Diabetics may be more likely referred to pre-operative internal medicine or anaesthesia clinics, allowing for enhanced medical optimization and post-operative follow-up. Our analysis of uninsured subjects demonstrated a loss of the protective association between uncomplicated diabetes and mortality and postoperative complications. Though this subgroup analysis does not confirm our speculation, it does confer credibility to the hypothesis. We should, however, note that there is sparse evidence in the literature to support the any clinically significant benefit of peri-operative medical consultation.[16]

Another possible explanation for our paradoxical findings may be that non-diabetics may have unrecognized and therefore untreated diabetes or other comorbidities. One study suggests that the true prevalence of hyperglycemia in hospitalized patients may be underestimated by as much as 40%.[17-19] Patients with newly diagnosed hyperglycemia have a higher mortality rate, longer length of stay, and increased rate of ICU transfers.[20] If the protective benefit of uncomplicated diabetes does arise from unrecognized comorbidity in the reference non-diabetic population, then we would expect to see less of a prominent effect among younger subjects who are less likely to have comorbid conditions. The lack of improved outcomes among uncomplicated diabetics younger than 50 years relative to their non-diabetic counterparts supports but does not confirm the above hypothesis.

We also found that the increased mortality rate associated with complicated diabetes relative to non-diabetics seemed to be limited to elective admissions only. In non-elective admissions, the urgent nature of the surgery may overshadow any benefit of being non-diabetic. For example, in Goldman et al's and Detsky et al.'s preoperative cardiac risk assessment tools, diabetes does not contribute to predicting increased risk in the face of more significant issues such as emergent-nature surgery or surgical site.[21-23] In Lee et al's Revised Cardiac Risk Index, diabetes needs to be sufficiently advanced to require insulin before being considered an independent predictor on par with having a "high-risk" surgical site.[24]

Another alternative explanation to our findings may be that uncomplicated diabetic subjects may be self-selected to be healthier than non-diabetics if they had relatively fewer comorbidities which may have resulted in fewer event rates among the former. However, this scenario is unlikely given that the Charlson Index was higher and specific non-diabetes comorbidities such as cardiovascular and renal disease were more common in the uncomplicated diabetic group than non-diabetics.

Our current study has several limitations inherent to administrative data analyses. The NIS data set does not contain personal identifiers that would allow linkage to medical records. We are unable to classify the severity of diabetes in patients and cannot assess what medications they were prescribed. Also, mortality was classified as all cause mortality and we are unable to break this down to specific causes. Furthermore, this is a cross-sectional study, and we are unable to longitudinally follow patients after discharge to assess long-term mortality and morbidity associated with diabetes post operatively.

One of the main limitations is the use of the ICD-9 codes to classify patients as having diabetes with and without complications. Studies assessing the accuracy and validity of ICD-9 codes for diabetes complications, quote up to 95% accuracy rates.[25,26] However, because the NIS contains de-identified subjects, it is not possible to validate diagnostic codes with the medical record for this dataset. Because diabetic complications were identified using administrative data, it is possible that

complicated diabetes may have been misclassified as uncomplicated diabetes. We would expect this misclassification to overestimate mortality and postoperative complications in the uncomplicated diabetes group and therefore biasing the odds ratio for mortality and complications relative to the non-diabetic group toward the null. Nonetheless, acknowledging these potential inaccuracies, we stratify analyses by the presence of complications only in secondary analyses.

The main strength of this study is the large sample size which offsets the possibility of a type I error induced by the multiple subgroup comparisons performed in this study. Additionally, this data set is a population-based representation of all hospitalized patients in the United States and reflects all types of hospital settings, insurance payers, and geographic regions, enhancing the generalizability of our data and minimizing referral bias associated with single-center studies from tertiary medical institutions.

Overall, our study illustrates that having uncomplicated diabetes unexpectedly appears to reduce post-operative complications in colorectal cancer surgical patients. It is important to note that, due to limitations of the administrative claims data, this study is intended to explore and generate new hypotheses in the field of peri-operative diabetic care. However, it would be premature to implement changes in the preoperative and inpatient management of diabetes based on these data alone. Thus, future prospective studies are necessary to replicate these results and establish these findings in other surgical groups. Additionally, primary studies are warranted to investigate the potential mechanisms underlying this seemingly paradoxical association. Such research may help identify practices that translate into meaningful reductions in surgical risk.

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Conflict of Interest: *Dr. Nguyen has served as a consultant for Schering Plough, Canada and Abbott Pharmaceutical, neither of whom had any involvement in this study. The other authors report no conflicts of interest.*

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