HHS Public Access

Author manuscript

Dis Colon Rectum. Author manuscript; available in PMC 2021 November 08.

Published in final edited form as:

Dis Colon Rectum. 2020 March ; 63(3): 290–299. doi:10.1097/DCR.0000000000001586.

Increased 30-day mortality risk in patients with diabetes following colon cancer surgery: a mediation analysis

Mario Schootman, Ph.D.[1,2], **Donna B. Jeffe, Ph.D.**[2,3], **Kendra L. Ratnapradipa, Ph.D.**[1], **Jan M. Eberth, Ph.D.**[4], **Nicholas O. Davidson, M.D., DSc.**[2,5]

[1]Saint Louis University, College for Public Health and Social Justice, Department of Epidemiology and Biostatistics.

[2]Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, Saint Louis, MO.

[3]Washington University School of Medicine, Department of Medicine, Division of General, Medical Sciences, Saint Louis, MO.

[4]University of South Carolina, Arnold School of Public Health, Department of Epidemiology and Biostatistics, Columbia, SC.

[5]Washington University School of Medicine, Department of Medicine, Division of Gastroenterology, Saint Louis, MO.

Abstract

BACKGROUND: Patients with (vs. without) diabetes who develop colon cancer are at increased risk of dying within 30 days following surgery.

OBJECTIVE: To identify potential mediators of the effect of diabetes on all-cause 30-day mortality risk after surgery for colon cancer.

DESIGN: A retrospective cohort study was conducted using the 2013–2015 National Surgical Quality Improvement Program data.

SETTING: Various hospitals across the United States (from 435 to 603 hospitals).

PATIENTS: Patients who underwent resection for colon cancer with or without obstruction based on the NSQIP colectomy module were included. Patients who had American Society of Anesthesiologists physical status classification V or metastatic disease and those who presented emergently were excluded. Patients were classified as “no diabetes”, “diabetes not requiring insulin”, or “diabetes requiring insulin.” Potential reasons for increased risk of dying within 30 days were treatment-related, comorbidity, health behaviors, surgical complications, and biomarkers of underlying disease.

Correspondence: Mario Schootman, PhD, SSM Health, 10101 Woodfield Lane, St. Louis, MO 63132. Mario.schootman@ssmhealth.com.

Author contributions: M.S. conceived and designed the study, acquired the data, analyzed the data and wrote the manuscript; D.B.J.: interpreted the findings, critically revised the manuscript, and helped design the study; K.R. and J.M.E. interpreted the findings and critically revised the manuscript; N.O.D. interpreted the findings, critically revised the manuscript, and helped design the study. M.S. is responsible for the overall content and accuracy of the manuscript.

Conflict of interest disclosures: No conflict of interest disclosures from any authors.

INTERVENTIONS: None.

MAIN OUTCOME MEASURES: All-cause 30-day mortality.

RESULTS: Of 26,060 patients, 18.8% (n=4,905) had diabetes that was treated with insulin (n=1,595) or other anti-diabetic agents (n=3,340). Patients with diabetes had a 1.57 (95% CI: 1.23–1.99) higher unadjusted odds of dying within 30 days versus patients without diabetes. In the multivariable model, 76.7% of the association between diabetes and 30-day mortality was explained; patients with diabetes were equally likely to die within 30 days versus those without diabetes (OR: 1.05; 95% CI: 0.81–1.35). Anemia and sepsis explained 33.7% and 15.2% of the effect of diabetes on 30-day mortality, respectively (each p<0.0001). Treatment-related variables, cardiovascular disease, surgical complications, and biomarkers played limited roles as mediators.

LIMITATIONS: limited to larger hospitals, and limited information about duration and type of diabetes.

CONCLUSIONS: Better management and prevention of anemia and sepsis among patients with diabetes may reduce their increased risk of death after colon cancer resection. See **Video Abstract** at http://links.lww.com/DCR/Axxx.

Abstract

Los pacientes con (y sin) diabetes que desarrollan cáncer de colon tienen un mayor riesgo de morir dentro de los 30 días posteriores a la cirugía.

Identificar los posibles mediadores del efecto de la diabetes sobre el riesgo de mortalidad dentro los 30 días, por cualquier causa después de cirugía por cáncer de colon.

Estudio de cohortes retrospectivo entre 2013–2015 utilizando los datos del Programa Nacional de Mejoría en Calidad Quirúrgica.

Entre 435 a 603 hospitales en los Estados Unidos

Se incluyeron aquellos pacientes sometidos a resección por cáncer de colon con o sin obstrucción según el módulo de colectomía NSQIP. Se excluyeron los pacientes estadío V de la clasificación de la Sociedad Estadounidense de Anestesiólogos (ASA), aquellos con enfermedad metastásica y aquellos operados de urgencia. Los pacientes se clasificaron como “sin diabetes”, “con diabetes que no requiere insulina” o “con diabetes que requiere insulina”. Las posibles razones para un mayor riesgo de morir dentro de los 30 días estuvieron relacionadas con el tratamiento, la comorbilidad, los comportamientos de salud, las complicaciones quirúrgicas y los biomarcadores de enfermedad.

Ninguna.

Mortalidad de cualquier orígen dentro los 30 días depués de la cirugía.

De 26’060 pacientes, 18.8% (n = 4,905) tenían diabetes tratada con insulina (n = 1,595) u otros agentes antidiabéticos (n = 3,340). Los pacientes con diabetes tenían 1.57 (IC 95%: 1.23–1.99) mayores probabilidades no ajustadas de morir dentro de los 30 días en comparación con los pacientes sin diabetes. En el modelo multivariable, se explicó que el 76,7% de la asociación entre diabetes y mortalidad a los 30 días; los pacientes con diabetes tenían la misma probabilidad de morir dentro de los 30 días que aquellos sin diabetes (OR: 1.05; IC 95%: 0.81–1.35). La anemia y la sepsis explicaron el 33,7% y el 15,2% del efecto de la diabetes en la mortandad a 30 días,

respectivamente (p <0,0001). Las variables relacionadas con el tratamiento, las enfermedades cardiovasculares, las complicaciones quirúrgicas y los biomarcadores jugaron un papel limitado como mediadores.

Estudio limitado a hospitales más grandes e información limitada sobre la duración y el tipo de diabetes.

Una mejor prevención y manejo de la anemia y la sepsis en los pacientes con diabetes puede reducir el mayor riesgo de muerte después de la resección del cáncer de colon. Ver **Video Resumen** en http://links.lww.com/DCR/Axxx.

Keywords

Anemia; Colon and rectal cancer; Diabetes mellitus; Mediation analysis; Prognosis; Sepsis

Introduction

Colorectal cancer (CRC) is the third most common cancer in the United States and accounts for nine percent of all cancer deaths.[1] Although evidence exists for the association between diabetes and increased risk of CRC incidence,[2] the impact of diabetes on 30-day mortality following CRC resection is less well established. Thirty-day mortality is a key quality measure of cancer care,[3] and variation in mortality among CRC patients undergoing surgery is especially pronounced during this time.[4] Patients with diabetes who develop CRC are more likely to die within 30 days compared to those without diabetes in some,[5,6] but not all studies.[7,8] However, most studies were conducted outside the United States, or sampled only a few hospitals with relatively few diabetic patients. Improved understanding of the association between diabetes mellitus and 30-day mortality risk following CRC resection has important implications for treating CRC patients with diabetes given the increasing prevalence of diabetes in the United States.

There is a need to understand the mechanisms that lead to worse prognosis among patients with diabetes in order to identify opportunities to reduce their risk of dying within 30 days of colon cancer resection.[9] Although direct empirical evidence is lacking, studies have suggested potential explanatory mechanisms through which diabetes increases risk of 30-day mortality following surgery, including surgical site infection and sepsis, anastomotic leakage, myocardial infarction, comorbidity, body-mass index (BMI), and different treatments for colon cancer.[5–7,10] In this study of a national sample of colon cancer patients, we examined 1) whether patients with diabetes were at increased risk of 30-day mortality following resection for colon cancer and 2) the extent to which the association between diabetes and 30-day mortality was mediated (aka explained) by type of treatment for colon cancer, surgical complications, comorbidity, biomarkers, and behavior. Mediation analysis is increasingly used in clinical research.[11,12] It is especially useful in observational studies like ours, because mediation analysis can provide causal explanations for the association between an exposure variable and outcome, which in this study is the association between diabetes and 30-day mortality.

MATERIALS AND METHODS

Data Source and patient selection

We used the 2013–2015 American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) Participant Use File and Targeted Colectomy File. The ACS-NSQIP measures the quality of surgical care by collecting patient-level data at participating hospitals. Additional details about the NSQIP can be found elsewhere https://www.facs.org/quality-programs/acs-nsqip). The Saint Louis University Institutional Review Board considered this study to be exempt from oversight. Preoperative patient characteristics, preoperative laboratory results, intraoperative procedure characteristics, surgical complications, and 30-day postoperative mortality rates were abstracted by trained reviewers from participating hospitals' medical records. Patients who underwent resection for nonemergent, nonmetastatic colon cancer (with or without obstruction) were included. Patients whose American Society of Anesthesiologists (ASA) physical status was class V (not expected to survive without surgery) and those with metastatic colon cancer were excluded from analysis because of their increased risk of 30-day mortality.

Diabetes status

Patient diabetes status was classified in the NSQIP data as "no diabetes" (no diagnosis of diabetes or diabetes controlled by diet alone), "diabetes not requiring insulin" (diabetes requiring therapy with a non-insulin anti-diabetic agent, such as oral agents or other non-insulin agents), or "diabetes requiring insulin" (diabetes requiring daily insulin therapy). Data about the time since first diabetes diagnosis and the type of diabetes were not available in the NSQIP data.

Patient outcome

All-cause 30-day mortality was operationalized as death within 30 days of resection obtained by NSQIP trained abstractors.

Potential mediators and confounders

Potential mediators and confounders were selected based on previous studies of prognostic factors of 30-day mortality among persons with diabetes or those diagnosed with colon cancer.[6,13–16] Mediators are variables that are hypothesized to be in the causal pathway between diabetes and 30-day mortality and must be associated with both diabetes and 30-day mortality; importantly, the exposure is presumed to cause the mediator, and the mediator is presumed to cause the outcome, and not vice versa.[17] The confounders also are associated with both diabetes and 30-day mortality but are not in the causal pathway and are not amenable to intervention (Figure 1). Potential mediators were categorized as treatment-related variables for colon cancer, comorbidities, behavior-related variables, surgical complications, and biomarkers of underlying disease. Potential confounders included patient demographic characteristics (sex, age group, Hispanic ethnicity, race, and year of surgery), which are not amenable to intervention.

Treatment-related variables included type of surgery (open, laparoscopic), mechanical bowel preparation (yes, no), preoperative antibiotic use (yes, no), chemotherapy (yes, no),

American Joint Commission on Cancer (AJCC) tumor node metastases (TNM) stage, and tumor location (left, right, other).

Comorbidities included patient functional status (partially dependent or totally dependent versus independent), hypertension, congestive heart failure, renal failure, preoperative loss of blood necessitating a transfusion, weight loss>10% in the last six months, and chronic obstructive pulmonary disease (COPD).[10] All were measured within 30 days prior to surgery.

Behavior-related variables included smoking status and BMI. A patient who had smoked cigarettes in the year prior to admission for surgery was considered a smoker. The patient's most recent height and weight, documented in the medical record within the 30 days prior to the colectomy or at the time the patient was being considered a candidate for surgery, was used to calculate BMI in kg/m^2. Patients were classified as underweight (BMI<18.5), normal weight (18.5≤BMI<25.0), overweight (25.0≤BMI<30.0), class 1–2 obesity (30.0≤BMI<40.0), or class 3 obesity (BMI≥40.0).

Surgical complications included readmission, reoperation, sepsis, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, blood transfusion, sum of infections (including surgical site, wound, and deep infections), anastomotic leakage, and prolonged postoperative ileus within 30 days. Presence of anastomotic leakage was determined if there was chart documentation, regardless of treatment interventions. Absence of a potential anastamotic leak was determined if there was no definitive diagnosis of a leak or related abscess documented in the chart. Readmission was defined as any readmission for any reason, (to the same or another hospital), within 30 days of the resection. Re-operation was defined as any unplanned return to the operating room for a surgical procedure, for any reason, within 30 days of surgery at any hospital or surgical facility. A wound infection included superficial or deep incisional surgical site infection or any other wound infection. Receipt of transfusion (yes/no) from the start of surgery to 72 hours post surgery was used as a measure of extensive blood loss.

Biomarkers included the following preoperative laboratory values with abnormal value cutoffs noted in parentheses: white blood cell count (≤4.5 or ≥11.0 × $10^3/\mu L$); glomerular filtration rate; serum albumin (3.0 mg/dL); serum alkaline phosphatase (>125 mg/dL); serum bilirubin (≥1.0 mg/dL); blood urea nitrogen (BUN, ≥40 mg/dL) and BUN-to-creatinine (BUN/creatinine, >20) ratio[18]; platelet count (150.0–450.0 × $10^3/\mu L$); partial thromboplastin time (>35); and preoperative hematocrit. Hematocrit values were treated as a categorical variable with the following cutoffs for anemia: severe (<25%), moderate (25% to <29%), mild (29% to <37%), and no anemia (≥37%).[19,20] Glomerular filtration rate (GFR) was calculated based on race, sex, age, and creatinine levels with a cutoff GFR>60 mL/min per 1.73 m^2.[21]

Statistical analysis

First, we tested the univariate associations between diabetes status and each potential mediator and demographic confounder using Chi-square tests. Second, we identified demographic variables that were confounders of the association between diabetes and 30-

day mortality or between a mediator and 30-day mortality for inclusion in the mediator models using logistic regression analysis.[11] Third, we determined the interaction between diabetes and the potential mediators.[22] Fourth, we determined which potential mediators were associated with diabetes status and 30-day mortality, adjusting for confounders, reporting odds ratios (OR) and 95% confidence intervals (CI).[22] Fifth, we used a decomposition method (KHB package in Stata/SE 14.2) to determine the extent to which each of the variables mediated the association between diabetes and 30-day mortality in separate single mediator models.[23–25] This is done by decomposing the total logit coefficient into its direct and indirect (mediated) parts and calculating a mediating percentage to assess the relative magnitude of direct and indirect effects, which can be given a causal interpretation.[23–25] The mediating percentage provides an estimate of the relative magnitude of the explanatory effect of each mediator separately on the association between diabetes and 30-day mortality risk and typically ranges from 0% (no mediating effect) to 100% (complete mediation). Negative mediating percentages mean that the mediator increased, rather than reduced, the OR (further away from the value of 1.0) between diabetes and 30-day mortality when included in the model. This could be due to an increase in 30-day mortality with an increase in the mediator or because a negative association exists between diabetes and the potential mediator. We used the Sobel test to determine if statistically significant ($p<0.05$) mediation existed (http://quantpsy.org/sobel/sobel.htm)[26,27]; this test determines whether the reduction in the effect of the diabetes on 30-day mortality risk is significant after adjusting for the mediator, and if so, the mediation effect is significant. Sixth, we used the KHB decomposition method to calculate the mediating percentage for each of the five categories of potential mediators. Finally, we used a single model with multiple mediators that were statistically significant using the Sobel test in single mediator models. This multiple-mediator model identified variables that significantly mediated the association of interest while adjusting for other mediators, confounders, and diabetes. The multiple-mediator approach allows the comparison of the magnitude of different mediators of the effect of diabetes on 30-day mortality risk.

RESULTS

Data were collected on 66,031 patients with colon resections in the 2013–2015 NSQIP. The primary indication for 36,734 of those patients was for non-metastatic colon cancer with or without obstruction; of those patients, we excluded from analysis 10,674 who were designated as ASA physical status class V, presented emergently and required surgery, or lacked data for type of surgery. In all, 26,060 patients were included in the analysis, 4,905 (18.8%) of whom had been diagnosed with diabetes mellitus requiring treatment with insulin (1,595 [6.1%]) or other anti-diabetic agents (3,340 [12.7%]). Table 1 shows that those with diabetes were more likely to be male, older, Hispanic, African American, hospitalized longer, overweight or obese, have comorbid conditions, have elevated adverse biomarkers, and to develop surgical complications. Patients with diabetes were less likely to receive chemotherapy, be diagnosed with cancer located in the left colon, and to smoke. The only demographic characteristic that acted as a confounder was age (Table 1). The other demographic characteristics were no longer confounders once age was included in the model. Many of the aforementioned characteristics increased the risk of 30-day mortality

when controlling for age. Characteristics that could not be mediators because they were not associated with diabetes and/or 30-day mortality included treatment-related variables (type of surgery, receipt of chemotherapy, stage at diagnosis, antibiotic prep), comorbidity (hypertension), biomarkers (white blood cell [WBC] count, albumin, alkaline phosphatase, partial thromboplastin time), and surgical complications (reoperation, deep vein thrombosis, pulmonary embolism, blood transfusion, surgical site infection, anastomotic leak, prolonged ileus). The interaction between diabetes and none of the potential mediators was statistically significant.

Overall, 30-day mortality was 1.4%, but was higher among patients with diabetes than those without diabetes (96 [2.0%] versus 266 [1.3%], respectively; $p<0.001$). In unadjusted analysis, patients with diabetes were 1.57 times more likely to die within 30 days than patients without diabetes (95% CI: 1.23–1.99). The difference in 30-day mortality between patients treated with insulin and those treated with other anti-diabetic agents was not significant (31 [1.9%] versus 65 [2.0%], respectively; $p=0.962$). Adjusting for age showed that patients with diabetes were 1.37 times more likely to die within 30 days of surgery than patients without diabetes (95% CI: 1.08–1.74).

Table 2 shows that several variables significantly mediated the association between diabetes and 30-day mortality based on the Sobel test, adjusting for the confounder, age. Of the comorbidity variables, functional status, congestive heart failure, renal failure, and Chronic Obstructive Pulmonary Disease (COPD) explained 18.7% of the association between diabetes and 30-day mortality. Because underweight, overweight, and obese patients were less likely to die within 30 days (Table 1), BMI increased rather than decreased the association between diabetes and 30-day mortality to 1.45 (95% CI: 1.14–1.86), but the Sobel test was not statistically different ($p=0.08$) indicating that BMI was not a mediator. Smoking mediated the association between diabetes and 30-day mortality for −4.2% ($p=0.006$) and slightly increased the OR for diabetes from 1.37 (95% CI: 1.08–1.74) to 1.38 (95% CI: 1.09–1.75). Significant biomarker mediators included hematocrit (26.2%) and BUN-creatinine ratio (10.4%). These biomarkers mediated the association between diabetes and 30-day mortality for 42.9%.

Table 3 shows that the significant mediators (shown in Table 2) based on the Sobel test explained 76.7% of the total association between diabetes and 30-day mortality. Patients with diabetes were as likely to die within 30 days versus those without diabetes (OR: 1.05; 95% CI: 0.81–1.35) in this multiple-mediator model. Of these variables, anemia explained 33.7% and sepsis explained 15.2% of the association between diabetes and 30-day mortality. Length of hospitalization, functional status, congestive heart failure, renal failure, BUN-creatinine ratio, and stroke explained less than 10% of the association between diabetes and 30-day mortality.

DISCUSSION

The purpose of this study was to identify mediators that explain the increased risk of 30-day mortality among patients with diabetes undergoing resection for nonemergent, nonmetastic colon cancer. Patients with diabetes had higher odds of dying within 30

days than patients without diabetes. Even though overall 30-day mortality was 1.4%, it was higher among patients with diabetes (2.0%) than those without diabetes (1.3%). These findings underscore the importance of recognizing and managing diabetes in all hospitalized patients, particularly those undergoing surgical interventions. Variables found to be significant mediators of this association between diabetes and 30-day mortality risk in single-mediator models, together explained 69.8% of this association in the multiple-mediator model. Among these mediators, anemia (30.8%) and sepsis (13.0%) had significantly large explanatory effects on the association between diabetes and 30-day mortality. After adjusting for all multiple mediators and the confounder, age, patients with (vs. without) diabetes were no longer at increased risk of dying within 30 days of colon resection OR: 1.06; 95% CI: 0.82–1.38). Identification of significant mediators can help inform targeted intervention efforts to reduce the elevated 30-day mortality risk after colon cancer resection among patients with diabetes.

Our results confirm the high prevalence of anemia and its prognostic value in colon cancer,[28,29] as well as the role of anemia as an important mediator of the association between diabetes and 30-day mortality. While the presence of anemia preoperatively may reflect blood loss, it may be due to lack of bone marrow production of red blood cells in the setting of chronic renal failure.[30] The prevalence of anemia in patients with diabetes mellitus is typically associated with presence of kidney disease.[31] While important among all colon cancer patients, appropriate screening, detection and treatment of both the anemia and underlying kidney disease are essential to improve the clinical outcomes particularly in colon cancer patients with diabetes.[32]

Our results also show that sepsis could explain the greater likelihood of 30-day mortality after colon cancer resection in patients with diabetes. Patients with diabetes were over 15 times more likely to die within 30 days if they developed sepsis. Other studies showed sepsis to be a prognostic factor following colon cancer resection and suggested more restrictive transfusion practices to reduce the risk of sepsis and improve survival.[33] However, for patients with anemia, other strategies may help avoid perioperative transfusions or reduce the risk of infection, including preoperative iron supplementation and reducing the storage time of blood.[34,35] Postoperative multidisciplinary care as managed by geriatricians also decreases the rate of surgical complications for older oncology patients.[36] Mild glycemic control may reduce the risk of death following sepsis.[37] Our results show that colon cancer patients with diabetes should be targeted especially.

Macrovascular disease is a major complication among persons with diabetes.[5] Contrary to other studies,[38] we found that stroke and congestive heart failure were also some of the reasons by which patients with diabetes were more likely to die following colon cancer resection. However, anemia and sepsis played more important roles. A recent meta analysis observed that very mild glycemic control reduced cardiovascular mortality.[37]

Despite assertions to the contrary,[5,6,10,38] our analysis also identified variables that were not significant mediators in the multiple-mediator model. Treatment-related variables (e.g., stage at diagnosis, type of surgical treatment), anastomotic leakage, comorbidity, and myocardial infarction, were not mediators. While these variables were associated with the increased risk

of 30-day mortality, they did not differ between patients with and without diabetes. As a result, they were not considered to be diabetes-specific mediators. Thus, while implementing interventions targeting these variables has been shown to reduce mortality, our findings suggest that the impact is unlikely to be confined to patients with diabetes after colon cancer resection.

We found that being overweight may provide benefits relative to being within the normal weight category. Because data on patients' post-diagnosis weight was not available in the NSQIP data, it was impossible to determine if patients subsequently lost weight, which could have a negative impact on patient outcomes. Others have suggested that heavier patients, who have greater muscle and fat mass, may better cope with the metabolic demands of tumor progression and treatment.[39] However, BMI was not a significant mediator of the association between diabetes and 30-day mortality (Sobel test, p=0.0745).

We recognize there are limitations of our study. We analyzed existing data available in the NSQIP database and therefore were limited to the data that the NSQIP collects; characteristics about NSQIP participating hospitals and surgeons, and data about other potential mediators with prognostic significance (e.g., depression, inflammation, hyperglycemia, physical activity, alcohol use), were not available. In addition, the NSQIP database typically includes data from larger hospitals and not from a nationally representative sample, limiting generalizability to smaller hospitals and hospitals that are not part of the NSQIP. The NSQIP data pertaining to diabetes did not include its duration and type of diabetes, and patients whose diabetes was managed without oral medications or insulin were classified in the 'no diabetes' group. Thus, we expect that the effect of diabetes status on 30-day mortality may be underestimated, since an estimated 30% of patients may have undiagnosed diabetes, and these patients were included in the no-diabetes group in the NSQIP database. Our study also had strengths, including the identification of actionable targets for why diabetic patients were at increased 30-day risk of dying after colon cancer surgery and use of the high-quality NSQIP data, which contained many potential mediators and confounders for a large sample of patients with diabetes.

CONCLUSION

In conclusion, oncologists, surgeons, and cancer patients should be aware of the excess postoperative mortality risk related to diabetes. Recognizing and optimizing management of diabetes in an increasingly obese and comorbid population is thus an important priority for hospitalized patients. Our findings suggest that managing anemia and preventing sepsis among patients with diabetes may reduce their increased risk of dying within 30 days after resection for nonmetastatic colon cancer.

Acknowledgments

Funding/Support: NOD was supported in part by NIH grants P30DK52574 (ARAC) and R01DK56260. JME was supported in part by MRSG-15-148-01-CPHPS from the American Cancer Society.

Financial Disclaimers: American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) and the hospitals participating in the ACS NSQIP are the sources of the data used herein; they have not

verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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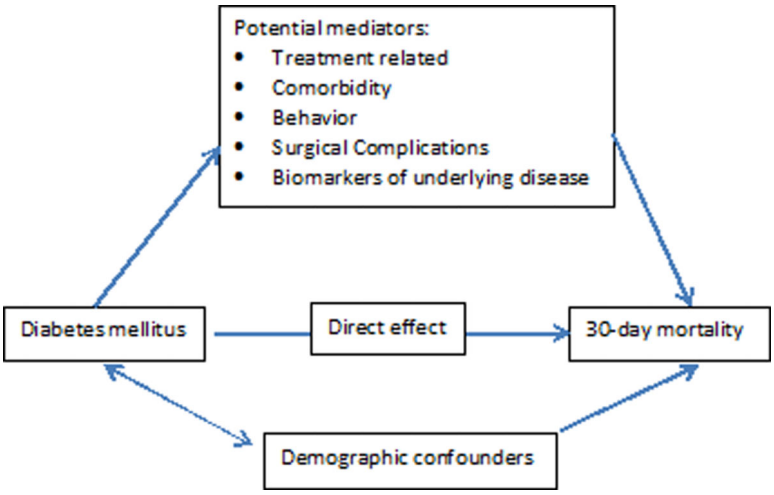

Figure 1.

Conceptual model of potential mediators and confounders for the association between diabetes and risk of 30-day mortality following colon resection. NOTE: A double-headed arrow refers to a nondirectional association, a single-headed arrow refers to variables predicting 30-day mortality

Table 1.

Study population characteristics in associations between each potential mediator and each of diabetes status and 30-day mortality among patients with nonmetastatic colon cancer following surgical resection.

Characteristic	Diabetes		Association between each potential mediator and DM adjusted for age group, OR (95% CI)	Association between each potential mediator and 30-day mortality adjusted for DM and age group, OR (95% CI)
	Yes (n=4,905) %	No (n=21,154) %		
Demographic confounders				
Sex (male) *	56.7	49.8	1.38 (1.29–1.47)	1.21 (0.98–1.49)
Age group *				
<45	1.3	6.8	Ref	Ref
45–54	9.1	16.5	2.89 (2.21–3.78)	1.49 (0.32–7.04)
55–64	22.7	23.1	5.13 (3.97–6.66)	4.69 (1.13–19.45)
65–74	34.4	24.6	7.31 (5.66–9.44)	7.92 (1.94–32.33)
75+	32.5	29.0	5.88 (4.55–7.60)	22.41 (5.56–90.30)
Hispanic ethnicity *	6.2	4.0	1.79 (1.56–2.05)	0.69 (0.35–1.34)
Race *				
White	67.0	73.2	Ref	Ref
African American	13.7	9.4	1.72 (1.56–1.89)	0.83 (0.56–1.23)
Other	5.9	4.7	1.46 (1.28–1.68)	0.71 (0.39–1.27)
Unknown	13.5	12.7	1.16 (1.05–1.27)	0.65 (0.45–0.93)
Treatment related mediators				
Type of surgery: Open vs laparoscopic	30.4	28.4	1.06 (0.99–1.14)	2.56 (2.08–3.16)
Mechanical bowel preparation *	57.2	57.2	1.08 (1.01–1.17)	0.44 (0.35–0.55)
Oral antibiotics	31.3	31.9	1.01 (0.94–1.08)	0.52 (0.40–0.68)
Chemotherapy *	7.8	10.4	0.86 (0.77–0.96)	0.79 (0.49–1.28)
TNM stage *				
0	1.8	2.2	Ref	Ref
I	15.7	14.6	1.15 (0.91–1.45)	3.09 (0.42–22.8)
II	17.3	17.4	0.99 (0.79–1.25)	5.15 (0.71–37.24)
III	16.4	17.9	0.96 (0.76–1.21)	5.18 (0.71–37.54)
Unknown	48.9	48.0	1.06 (0.85–1.32)	6.70 (0.94–48.00)
Tumor location *				
Left	37.3	41.7	Ref	Ref
Right	41.1	35.8	1.10 (1.02–1.18)	1.05 (0.81–1.37)
Transverse	21.6	22.5	1.00 (0.92–1.09)	1.75 (1.34–2.31)
Comorbidity mediators				
Functional status *	4.3	2.4	1.59 (1.35–1.87)	3.98 (2.93–5.40)
Hypertension *	81.7	47.3	4.55 (4.20–4.93)	1.15 (0.91–1.46)

Characteristic	Diabetes		Association between each potential mediator and DM adjusted for age group, OR (95% CI)	Association between each potential mediator and 30-day mortality adjusted for DM and age group, OR (95% CI)
	Yes (n=4,905) %	No (n=21,154) %		
Congestive heart failure *	2.6	1.1	2.05 (1.65–2.56)	4.07 (2.72–6.08)
Renal failure *	1.5	0.5	3.13 (2.30–4.26)	2.25 (0.98–5.16)
Preoperative loss of blood necessitating transfusion *	13.3	9.6	1.31 (1.19–1.44)	3.87 (3.10–4.83)
Weight loss>10% *	4.7	5.4	0.85 (0.74–0.99)	2.12 (1.51–2.98)
COPD *	6.9	5.2	1.19 (1.05–1.35)	2.59 (1.95–3.44)
Behavioral mediators				
BMI, kg/m^2 *				
<18.5	0.9	2.7	1.76 (1.28–2.43)	0.41 (0.26–0.63)
18.5–24.9	17.7	32.8	Ref	Ref
25.0–29.9	29.9	34.6	2.94 (2.14–4.05)	0.28 (0.18–0.44)
30.0–39.9	40.6	25.6	5.79 (4.21–7.97)	0.29 (0.18–0.47)
40.0+	11.0	4.3	10.57 (7.57–14.77)	0.47 (0.26–0.87)
Smoking *	10.2	13.8	0.81 (0.73–0.90)	1.85 (1.36–2.51)
Biomarker-related mediators				
Abnormally low or high WBC count *	16.8	17.6	0.96 (0.88–1.05)	1.85 (1.46–2.34)
Glomerular filtration rate *	28.5	15.8	1.75 (1.62–1.89)	1.55 (1.24–1.95)
Abnormally high albumin *	7.5	6.7	0.98 (0.87–1.11)	4.54 (3.56–5.79)
Abnormally high alkaline phosphatase	32.9	33.1	1.01 (0.95–1.08)	1.01 (0.81–1.26)
Abnormally high bilirubin *	5.3	6.9	0.73 (0.63–0.83)	1.83 (1.32–2.54)
Abnormally high BUN *	3.0	0.9	2.74 (2.20–3.40)	3.98 (2.62–6.03)
Abnormally high BUN-creatinine ratio *	23.6	19.3	1.39 (1.11–1.74)	1.38 (1.10–1.74)
Abnormally low platelet count *	7.3	5.6	1.24 (1.09–1.40)	1.97 (1.44–2.70)
Abnormally high partial thromboplastin * time	5.3	4.1	1.10 (0.95–1.27)	1.52 (1.03–2.24)
Preoperative low hematocrit *				
Severe	2.3	1.7	1.52 (1.22–1.89)	4.80 (2.97–7.75)
Moderate	10.4	7.0	1.72 (1.54–1.93)	2.69 (1.91–3.80)
Mild	43.3	33.4	1.54 (1.44–1.65)	2.18 (1.69–2.81)
No anemia	41.6	54.3	Ref	Ref
Unknown	2.3	3.6	0.83 (0.68–1.02)	0.34 (0.08–1.40)
Complication-related mediators				
Readmission *	11.5	9.5	1.22 (1.11–1.35)	1.79 (1.35–2.37)
Reoperation	5.0	4.4	1.15 (0.99–1.33)	7.30 (5.66–9.44)
Sepsis *	4.6	3.5	1.31 (1.12–1.53)	15.86 (12.54–20.04)

Characteristic	Diabetes		Association between each potential mediator and DM adjusted for age group, OR (95% CI)	Association between each potential mediator and 30-day mortality adjusted for DM and age group, OR (95% CI)
	Yes (n=4,905) %	No (n=21,154) %		
Deep vein thrombosis	1.3	1.2	1.04 (0.79–1.37)	3.89 (2.37–6.38)
Pulmonary embolism	1.0	0.7	1.28 (0.92–1.78)	4.81 (2.74–8.45)
Myocardial infarction *	1.1	0.7	1.28 (0.94–1.75)	11.31 (7.74–16.54)
Stroke *	0.6	0.3	1.96 (1.24–3.09)	11.01 (6.23–19.46)
Blood transfusion *	3.7	2.9	1.14 (0.96–1.34)	2.15 (1.47–3.14)
One or more infections *	7.8	5.6	1.42 (1.26–1.61)	2.06 (1.48–2.86)
Anastomotic leak	3.8	3.5	1.13 (0.95–1.33)	7.31 (5.49–9.73)
Prolonged ileus *	15.2	14.3	1.03 (0.94–1.12)	4.78 (3.87–5.90)

* $p<0.05$ between patients with and those without diabetes based on Chi-square test

Table 2.

Percentage (%) of the effect of diabetes on 30-day mortality following colon resection that is explained by each mediating variable in single mediator models and risk of 30-day mortality due to diabetes controlling for each mediator or blocks of mediators.*

Potential mediator	Percentage of the effect of diabetes on 30-day mortality explained by the mediator	P value for the Sobel test of the hypothesis that the mediated effect is zero	Odds of 30-day mortality associated with diabetes, adjusted for each mediating factor, OR (95% CI)
Treatment related			
Mechanical bowel preparation	−1.0	0.2302	1.36 (1.08–1.73)
All treatment mediators combined with Sobel test p<0.05			
Comorbidity			
Functional status	7.9	<0.0001	1.29 (1.02–1.64)
Congestive heart failure	6.3	<0.0001	1.30 (1.03–1.66)
Renal failure	2.7	0.0449	1.34 (1.06–1.70)
Preoperative loss of blood necessitating transfusion	1.1	0.8578	1.35 (1.07–1.71)
COPD	3.1	0.0059	1.35 (1.07–1.71)
Weight loss >10%	−1.8	0.0588	1.37 (1.08–1.74)
All individual comorbidity mediators combined with Sobel test p<0.05	*18.7*		*1.23 (0.97–1.57)*
Behavior			
BMI (kg/m^2)	−12.2	0.0745	1.45 (1.14–1.86)
Smoking	−4.2	0.0062	1.38 (1.09–1.75)
All behaviors combined with Sobel test p<0.05	−4.2		1.38 (1.09–1.75)
Biomarkers			
Abnormally low platelet count	−0.1	0.8494	1.36 (1.07–1.72)
Preoperative hematocrit	26.2	<0.0001	1.26 (0.99–1.60)
Abnormally high bilirubin	1.5	0.0770	1.35 (1.07–1.72)
Glomerular filtration rate	2.3	0.1048	1.34 (1.06–1.71)
BUN	2.8	0.1307	1.36 (1.07–1.72)
BUN-Creatinine ratio	10.4	0.0320	1.34 (1.05–1.69)
All biomarkers combined with Sobel test p<0.05	*42.9*		*1.21 (0.95–1.54)*
Complications			
Readmission	3.6	0.0042	1.34 (1.06–1.70)
Sepsis	11.8	0.0006	1.24 (0.97–1.59)
Stroke	2.4	0.0030	1.32 (1.04–1.67)
One or more infections	5.1	0.0005	1.34 (1.06–1.70)
All complications combined with Sobel test p<0.05	*17.5*		*1.20 (0.94–1.54)*

*Each model controlled for age as a confounder. Variables that were not associated with diabetes status and 30-day mortality in Table 1 were not included, because they cannot be mediators. These variables included: type of surgery, receipt of chemotherapy, TNM stage, tumor location, hypertension, abnormally high or low WBC, albumin, alkaline phosphatase, partial thromboplastin time, deep vein thrombosis, pulmonary embolism, blood transfusion, anastomotic leak, and prolonged ileus.

Table 3.

Percentage of the effect of diabetes on 30-day mortality following colon resection that is explained by each mediating variable in a multiple-mediator model adjusted for age group, NSQIP 2013–2015.

Mediators*	Percentage of the effect of diabetes on 30-day mortality explained by the mediator	P value of the hypothesis that the mediated effect is zero
Anemia	33.7	0.0001
Sepsis	15.2	0.001
Functional status	7.1	0.0005
High BUN-creatinine ratio	6.3	0.0009
BUN-creatinine ratio unknown	6.4	0.20
Congestive heart failure	5.6	0.003
COPD	3.6	0.03
Stroke	3.0	0.04
Renal failure	1.1	0.66
One or more infections	0.2	0.93
Readmission	−1.5	0.36
Smoking	−3.9	0.09
Total mediating effect	76.7	

*Variables that were mediators of the association between diabetes and 30-day mortality based on the Sobel test from the single-mediator models in Table 2.