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High and low estimated glomerular filtration rates are associated with adverse outcomes in patients undergoing surgery for gastrointestinal malignancies

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ABSTRACT

Background. Abnormally high estimated glomerular filtration rates (eGFRs) are associated with endothelial dysfunction and frailty. Previous studies have shown that low eGFR is associated with increased morbidity, but few reports address high eGFR. The purpose of this study is to evaluate the association of high eGFR with surgical outcomes in patients undergoing surgery for gastrointestinal malignancies.

Methods. We identified patients who underwent elective surgery for gastrointestinal malignancies from 2005 to 2015 in the American College of Surgeons National Surgical Quality Improvement Program database. We evaluated associations of eGFR with surgical outcomes by Cox or logistic models with restricted cubic spline functions, adjusting for case mix variables (i.e. age, gender, race and diabetes).

Results. The median eGFR is 83 (interquartile range 67–96) mL/min/1.73m². Thirty-day mortality was 1.9% (2555/136 896). There is a U-shaped relationship between eGFR and 30-day mortality. The adjusted hazard ratios (95% confidence intervals) for eGFRs of 30, 60, 105 and 120 mL/min/1.73m² (versus 90 mL/min/1.73m²) are 1.73 (1.52–1.97), 1.00 (0.89–1.11), 1.42 (1.31–1.55) and 2.20 (1.79–2.70), respectively. Similar associations are shown for other surgical outcomes, including return to the operating room and postoperative pneumonia. Subgroup analyses show that eGFRs both higher and lower than the respective medians are consistently associated with a higher risk of adverse outcomes across age, gender and race.

Conclusions. High and low eGFRs are associated with more adverse surgical outcomes in patients undergoing surgery for gastrointestinal malignancies. The eGFR associated with the lowest postoperative risk is approximately at the median eGFR of a given population.

Keywords: 30-day mortality, CKD-EPI, estimated glomerular filtration rate, gastrointestinal malignancies, surgical outcomes

INTRODUCTION

Gastrointestinal malignancies are the most common type of cancer, with >150 000 patients dying of gastrointestinal cancers in the USA in 2016 [1]. Surgical outcomes for patients with gastrointestinal cancer have improved by refining pre- and postoperative management and advances in surgical techniques [2]. Although the incidence of postoperative complications in patients with gastrointestinal cancer has progressively decreased, mortality has not significantly improved [3]. In addition, postoperative morbidity adversely affects long-term oncologic outcomes [4]. Further improvements in surgical outcomes are imperative to minimize morbidity and mortality and thus improve overall outcomes in patients with gastrointestinal malignancies.

Previous studies reported that renal insufficiency is an independent predictor of postoperative mortality and morbidity for a number of surgical procedures [5–12]. However, among nonsurgical patients, high estimated glomerular filtration rate (eGFR) levels have also been associated with greater mortality, resulting in a U-shaped association of eGFR with mortality [13–16]. A recent study also revealed a relationship between high eGFR and respiratory complications after laparoscopic surgery [17], but data related to gastrointestinal cancer are scarce.

We hypothesized that high eGFR levels as well as low eGFR levels are associated with adverse postoperative outcomes in patients undergoing surgery for gastrointestinal malignancies.

MATERIALS AND METHODS

Database

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database was developed through NSQIP, which was started in the 1990s by the Veterans Health Administration [18, 19]. The ACS-NSQIP database collects patient data for hospital inpatients as well as 30-day outcome data on surgical patients from >370 hospitals throughout the USA [2, 20].

Patient selection

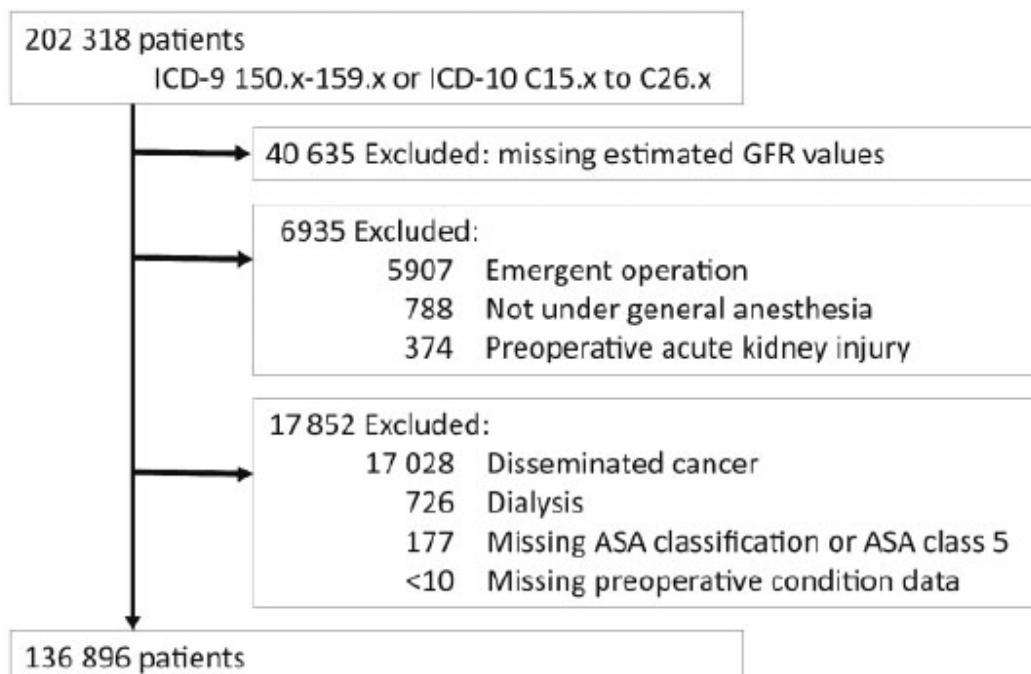
We identified 202 318 patients who underwent surgery for gastrointestinal malignancies from 2005 to 2015 based on the International Classification of Diseases (ICD) codes (i.e. 150.x– 159.x in ICD-9 or C15.x– C26.x in ICD-10). Patients without data for eGFR calculation were excluded. Patients who underwent emergent operations, those who did not receive general anesthesia and those with preexisting acute kidney injury were also excluded. Finally, patients with disseminated cancer, those on maintenance dialysis, those classified as American Society of Anesthesiologists (ASA) Class 5 moribund and those without preoperative condition data were also excluded. The final study cohort included the remaining 136 896 patients (Figure 1).

Study variables

The exposure of interest was eGFR calculated using preoperative serum creatinine, age, gender and race based on the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) formula [21, 22]. Patients were categorized into six groups according to eGFR levels; <30, 30–<60, 60–<90, 90–<105, 105–<120 and ≥ 120 mL/min/1.73m².

Primary outcomes of interest were all-cause 30-day postoperative mortality, return to the operating room and postoperative pneumonia. Secondary outcomes included deep vein thrombosis (DVT) or thrombophlebitis, the need for blood transfusion and urinary tract infection.

FIGURE 1: Study flow diagram (American College of Surgeons National Surgical Quality Improvement Program).



Statistical analysis

Preoperative characteristics are expressed as mean \pm standard deviation (SD), median [interquartile range (IQR)] or percentages, as appropriate. Differences between included and excluded patients were compared by standardized differences, due to the large sample size of this study [23, 24]. Trends in each patient characteristic across eGFR categories were evaluated by nonparametric tests.

We estimated the risk associated with eGFR levels using a Cox proportional hazards model for all outcomes except for return to the operating room, where we used a logistic regression model because of a lack of time-to-event data. eGFR was modeled as a continuous variable using restricted cubic spline functions with a reference at 90mL/min/1.73m² and four knots at the 5th, 35th, 65th and 95th percentiles of eGFR. Three levels of adjustment were used: (1) unadjusted models, (2) case mix adjusted models that included demographics [i.e. age, gender, race (nonblack versus black)] and diabetes and (3) fully adjusted models that included all covariates in the case mix model plus preoperative conditions including body mass index (BMI), hypertension, ventilator dependent, wound infection, steroid use for chronic condition, >10% loss of body weight in 6 months, ascites, bleeding disorder, preoperative transfusion, ASA classification, serum albumin and type of cancer.

In order to examine the effect of modifications on the association of eGFR with the primary outcomes, we conducted subgroup analyses according to age (<65 versus \geq 65 years), gender, race (nonblack versus black), BMI (<30 versus \geq 30 kg/m²), diabetes and cancer type. We evaluated the statistical significance of effect modification by the log-likelihood ratio test comparing models both with and without the interaction terms between a given variable and the spline functions of eGFR in the case mix-adjusted model. We also evaluated the eGFR-outcome associations using the median eGFR level as a reference in each stratum of age, gender and race.

The frequency of missing values was 20% and 0.6% for serum albumin and BMI, respectively, and multiple imputations with five sets were done using a multivariate normal regression based on all baseline data and indicators of outcomes. We demonstrated that the relationship between eGFR and the primary outcomes of interest was maintained, even when patients with missing albumin values were excluded. We conducted all analyses with Stata IC version 14.2 (StataCorp, College Station, TX, USA) and P-values <0.05 were considered statistically significant.

RESULTS

Patient demographic, clinical and laboratory characteristics

Among 136 896 patients who underwent surgery for gastrointestinal malignancies between 2005 and 2015, the median eGFR was 83 (IQR 67–96) mL/min/1.73m². The overall 30-day mortality was 1.9% (2555/136 896). The mean age (\pm SD) was 65 \pm 13 years, 46% were female and 11% were black (Table 1). The prevalences of eGFR <30, 30–<60, 60–<90, 90–105, 105–<120 and \geq 120mL/min/1.73m² were 1.4% (n = 1880), 16% (n = 22 280), 46% (n = 63 061), 25% (n = 34 762), 8.8% (n = 12 082) and 2.1% (n = 2831), respectively. Patients with a high eGFR were typically younger, black and had a history of tobacco abuse, in addition to having a lower BMI and a lower prevalence of diabetes, hypertension, chronic obstructive pulmonary disease, congestive heart failure, chronic heart failure, acute renal failure and steroid use. The overall incidences of 30-day mortality, returning to the OR, pneumonia, DVT or thrombophlebitis, blood transfusion and urinary tract infection were 1.9% (n = 2555), 5.7% (n = 7799), 3.4% (n = 4633), 1.7% (n = 2307), 11% (n = 14 746) and 3.2% (n = 4403), respectively (Table 2).

Relationship between eGFR and surgical outcomes

Although patients with a high eGFR experienced lower 30-day postoperative mortality using an unadjusted model, we observed a U-shaped relationship between 30-day mortality and eGFR in the case mix-adjusted model adjusted for age, gender, race and diabetes (Figure 2). The case mix-adjusted hazard ratios (HRs) for 30-day mortality at eGFRs of 30, 60, 105 and 120mL/min/1.73m² (versus 90mL/min/1.73m²) were 1.73 [95% confidence interval (CI) 1.52–1.97], 1.00 (0.89–1.11), 1.42 (1.31–1.55) and 2.20 (1.79–2.70), respectively. The adjusted odds ratios (ORs) for return to the operating room were 1.07 (95% CI 0.93–1.23), 0.98 (0.92–1.04), 1.14 (1.08–1.40) and 1.34 (1.17–1.52) at eGFRs of 30, 60, 105 and 120mL/min/1.73m² (versus 90mL/min/1.73m²), respectively. Corresponding adjusted HRs for postoperative pneumonia were 1.21

Table 1. Baseline characteristics of 136 896 patients with gastrointestinal malignancies who underwent operations categorized by eGFR, from 2005 to 2015

Variables	eGFR at baseline (mL/min/1.73 m ²)						P-value	
	Total cohort (n = 136896)	<30 [n = 1880 (1.4%)]	30–60 [n = 22 280 (16%)]	60–90 [n = 63 061 (46%)]	90–105 [n = 34 762 (25%)]	105–120 [n = 12 082 (8.8%)]		≥120 [n = 2831 (2.1%)]
Age (years), mean ± SD	65 ± 13	74 ± 10	75 ± 9	68 ± 11	60 ± 10	51 ± 10	44 ± 12	<0.001
Gender (female), %								
Female	46	54	51	45	43	45	47	<0.001
Race, %								
Nonblack	89	86	91	91	91	76	50	<0.001
Black	11	14	8.9	8.8	9.1	24	50	<0.001
BMI (kg/m ²), mean ± SD	28.2 ± 6.4	29.1 ± 6.6	28.8 ± 6.5	28.2 ± 6.2	28.0 ± 6.4	27.8 ± 7.1	27.1 ± 7.7	<0.001
Smoking, %	17	10	10	14	23	31	33	<0.001
Comorbidity, %								
Diabetes	20	39	29	19	18	16	15	<0.001
Hypertension	55	85	78	58	44	33	26	<0.001
Chronic obstructive pulmonary disease	5.6	10	7.8	5.8	4.7	3.6	2.5	<0.001
Congestive heart disease	0.9	4.9	2.0	0.8	0.4	0.3	0.3	<0.001
Ventilator dependent	<0.1	0.3	<0.1	<0.1	<0.1	<0.1	0.2	0.61
Wound infection	1.1	2.6	1.2	1.0	1.0	1.4	2.5	0.053
Steroid use	2.7	5.8	3.9	2.6	2.3	2.3	2.6	<0.001
>10% loss of body weight	9.3	6.6	6.9	8.0	11	14	18	<0.001
Ascites	0.8	1.2	0.8	0.7	0.9	1.1	1.9	<0.001
Bleeding disorder	3.8	5.9	5.5	3.8	3.0	2.7	3.5	<0.001
Transfusion of red blood cells	1.8	3.8	2.4	1.6	1.6	1.8	3.2	0.001
Infection present at time of surgery	0.8	1.3	0.7	0.7	0.8	0.9	1.8	<0.001
ASA classification, %								
I	1.4	<0.1	0.4	1.3	1.8	2.4	3.1	<0.001
II	34	11.0	22	35	39	41	39	<0.001
III	59	70	69	59	55	53	53	<0.001
IV	5.8	20	10	5.3	4.2	3.9	5.4	<0.001
Lab results								
Creatinine (mg/dL), median (IQR)	0.90 (0.71–1.04)	2.30 (1.95–2.78)	1.27 (1.10–1.41)	0.90 (0.80–1.01)	0.73 (0.66–0.83)	0.68 (0.60–0.75)	0.60 (0.50–0.70)	<0.001
Albumin (g/dL), mean ± SD	3.77 ± 0.61	3.51 ± 0.63	3.69 ± 0.59	3.81 ± 0.59	3.80 ± 0.61	3.73 ± 0.65	3.56 ± 0.71	<0.001
Cancer, %								
Esophagus and stomach	9.0	6.6	7.3	8.6	10	10	9.6	<0.001
Colon and rectum	64	73	70	65	59	59	60	<0.001
Liver and bile duct	8.0	7.1	7.4	7.9	8.7	8.5	8.1	<0.001
Pancreas	15	9.1	12	15	18	17	16	<0.001
Others	4.0	3.8	3.8	3.8	4.1	4.4	6.0	<0.001

Table 2. Frequency of complications in patients with gastrointestinal malignancies

Complication (%)	Missing (%)	Total cohort <i>n</i> = 136 896	Estimated GFR at baseline						P-value
			<30 <i>n</i> = 1880 (1.4%)	30–60 <i>n</i> = 22 280 (16%)	60–90 <i>n</i> = 63 061 (46%)	90–105 <i>n</i> = 34 762 (25%)	105–120 <i>n</i> = 12 082 (8.8%)	>120 <i>n</i> = 2831 (2.1%)	
30-day postoperative mortality	0	2555 (1.9)	80 (4.3)	705 (3.2)	1115 (1.8)	475 (1.4)	147 (1.2)	33 (1.2)	<0.001
Return to operating room	0	7779 (5.7)	125 (6.6)	1245 (5.6)	3400 (5.4)	2011 (5.8)	779 (6.4)	219 (7.7)	<0.001
Pneumonia	0	4633 (3.4)	110 (5.9)	919 (4.1)	2037 (3.2)	1095 (3.1)	379 (3.1)	93 (3.3)	<0.001
DVT/thrombophlebitis	0	2307 (1.7)	40 (2.1)	393 (1.8)	1059 (1.7)	565 (1.6)	188 (1.6)	62 (2.2)	0.34
Bleeding transfusions	0	14 746 (11)	402 (21)	3005 (13)	6107 (9.7)	3447 (9.9)	1379 (11)	406 (14)	<0.001
Urinary tract infection	0	4403 (3.2)	76 (4.0)	896 (4.0)	2012 (3.2)	948 (2.7)	376 (3.1)	95 (3.4)	<0.001

GFR, glomerular filtration rate.

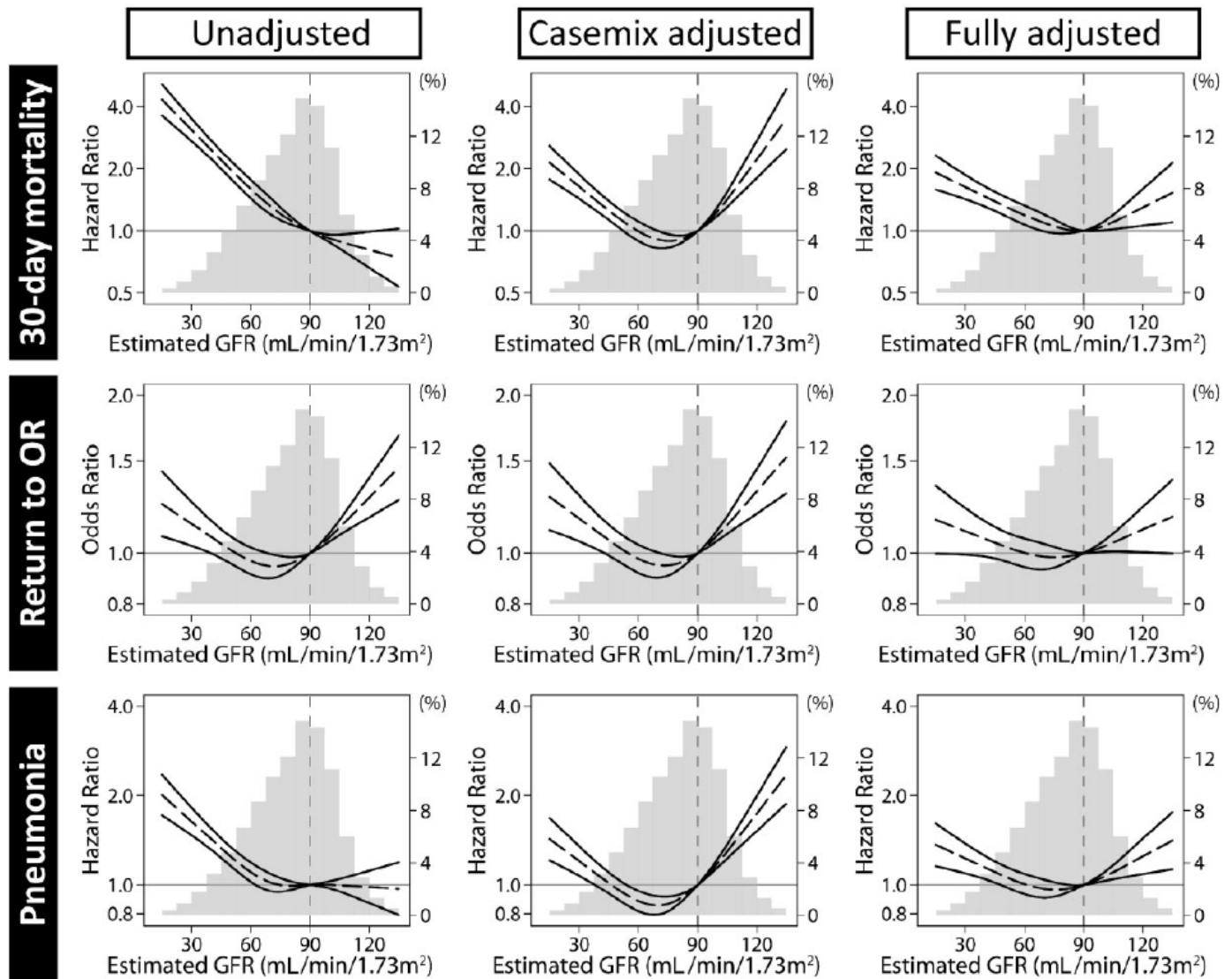


FIGURE 2: The associations between complications and eGFR with three-level adjustments. Vertical lines at 90 mL/min/1.73m² of estimated GFR indicate the reference value. Analysis of 30-day mortality, return to operating room and pneumonia.

(95% CI 1.08–1.36), 0.88 (0.82–0.95), 1.30 (1.23–1.37) and 1.74 (1.52– 1.99) at eGFRs of 30, 60, 105 and 120mL/min/1.73m² (versus 90mL/min/1.73m²), respectively. The U-shaped associations between eGFR and adverse outcomes were consistently observed for bleeding requiring transfusion. The risks of urinary tract

infection and the composite of DVT and thrombophlebitis are higher in high eGFR than in low eGFR patients. The U-shaped curves of all outcomes persisted in the fully adjusted model (Figure 2; Supplementary data, Figure S1). The U-shape of curves of all outcomes was maintained when patients with missing albumin values were excluded. (Supplementary data, Figure S2)

Subgroup analysis for 30-day mortality, return to the operating room and pneumonia

Subgroup analyses to evaluate the association between eGFR and 30-day mortality, return to the operating room and pneumonia were performed across age, gender, race, obesity, diabetes and cancer type (Figure 3; Supplementary data, Table S1). Age and type of malignancy significantly modified the risk associated with eGFR for all outcomes (P for log-likelihood ratio test <0.05). The risk associated with low eGFR is more pronounced for younger than for older patients. High and low eGFR are both associated with an increased risk of adverse outcomes in patients undergoing colorectal surgery. Pancreas surgery in patients with a low eGFR is associated with an increased risk of postoperative complications, while pancreas surgery in patients with a high eGFR is not associated with an increased risk of postoperative complications.

Given that eGFR calculations are made using variables such as age, gender and race and given that the distribution of eGFR varies across the subgroups of these components, we conducted additional subgroup analyses using the median eGFR level as a reference to further elucidate the association between eGFR and outcomes (Figure 4). The median eGFR was lower in patients ≥ 65 years of age (74 versus 94 mL/min/1.73m² in younger patients), females (82 versus 84 mL/min/1.73m² in males), and nonblacks (83 versus 89 mL/min/1.73m² in blacks). The association of eGFRs with primary outcomes consistently showed a U- or J-shaped association. Patients having an eGFR at the median level had the lowest risk of postoperative complications.

DISCUSSION

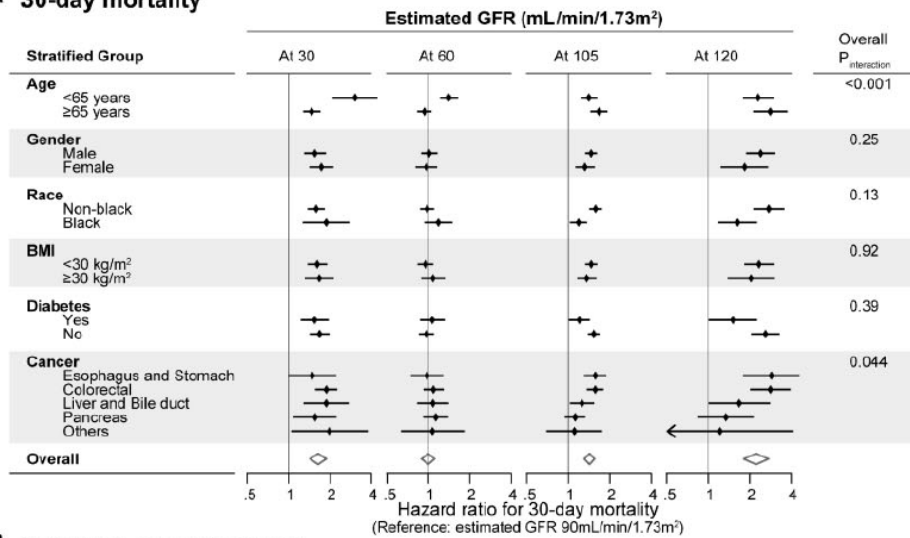
This study examined the association of surgical outcomes with preoperative eGFR in patients undergoing operations for gastrointestinal malignancies. This is the first study to demonstrate that the adjusted risk of adverse postoperative outcomes is consistently higher in patients with high eGFR as well as in patients with low eGFR.

The mechanism resulting in worse outcomes in patients with low eGFR can be at least partially explained by the tendency toward fluid accumulation. Patients with kidney dysfunction have an impaired ability to concentrate or dilute urine, which can lead to adverse consequences in the setting of postoperative fluid administration [25, 26]. In addition, patients with decreased kidney function are at a higher risk for acute kidney injury and are more likely to suffer adverse effects from the many drugs they may require during the postoperative period [10, 27].

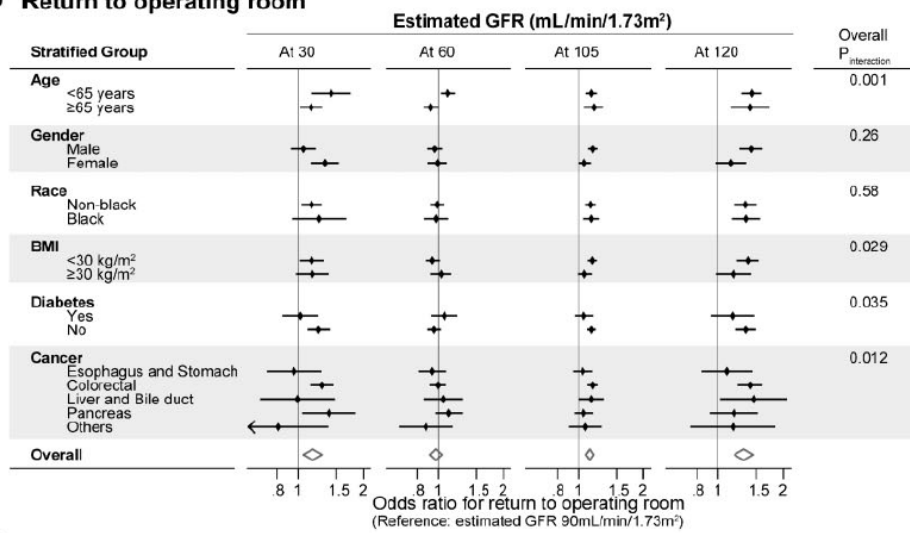
The risk associated with high eGFR may be further partially explained by frailty and glomerular hyperfiltration [15]. Creatinine is a nonprotein waste product of creatine phosphate metabolism by skeletal muscle, and the rate of creatine production is lower among individuals with less muscle mass, resulting in a lower serum creatinine concentration. Hence serum creatinine 1533 Bonner Springs Drive based eGFR is well known to overestimate actual kidney function in frail subjects [28–30]. Muscle wasting and weakness result in a higher likelihood of adverse events after surgery [31–35]. A loss of muscle mass may reflect a state of prolonged catabolism impairing host immune function. Therefore, frailty is related to diminished systemic inflammatory response and an increased rate of adverse events [36, 37]. Glomerular hyperfiltration is a possible factor in the pathogenesis of diabetic kidney disease and can be caused by various clinical conditions such as obesity, hypertension and sleep apnea [38–42]. Although there is no consensus on the definition of glomerular hyperfiltration [43], glomerular hyperfiltration is often defined as >120 mL/min/1.73m² or eGFR $>90^{\text{th}}$ percentile [42, 44, 45]. Glomerular hyperfiltration has been linked with systemic vascular abnormalities, endothelial dysfunction and vasoactive mediators [42]. These systemic factor/mediators and underlying glomerular hyperfiltration may partially explain the positive correlation between high eGFR and the increased incidence of postoperative adverse outcomes.

These postulated mechanisms for disease progression based on frailty and glomerular hyperfiltration support the finding that the lowest risks for adverse surgical outcomes were observed approximately at the median eGFR level in a given population. Kidney function and muscle mass varies according to age, gender and race [21, 30, 46] and hence the associations of eGFR with frailty and hyperfiltration are likely to be dependent

A 30-day mortality



B Return to operating room



C Pneumonia

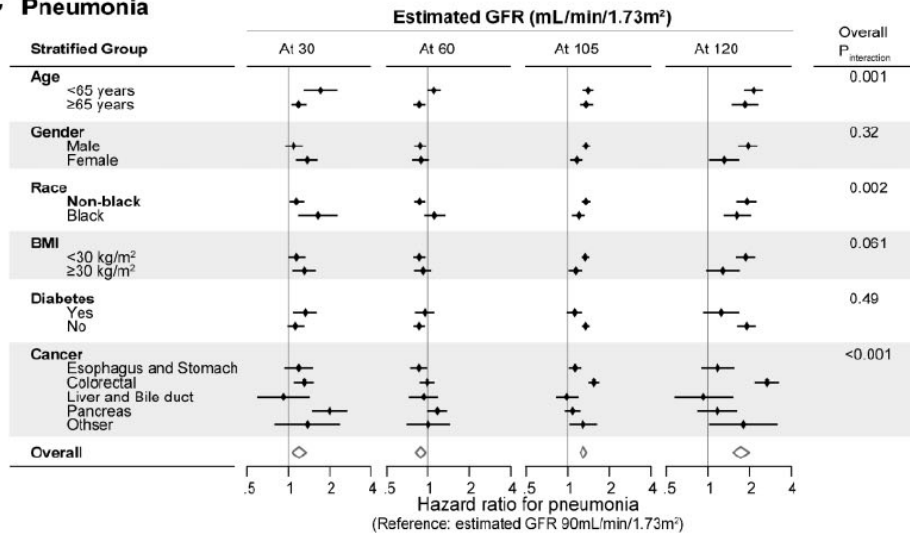


FIGURE 3: Association of eGFR with (A) 30-day mortality, (B) return to the operating room and (C) pneumonia by age, gender, race, BMI (<30, ≥30 kg/m²), diabetes and type of malignancy. Lines represent HRs for 30-day mortality for patients with each value (reference: 90 mL/min/1.73m²). Cox proportional hazards models with restricted spline function were evaluated for 30-day mortality and pneumonia with adjustments for age, gender, race and diabetes. A logistic regression model was evaluated for return to the operating room with the same adjustments.

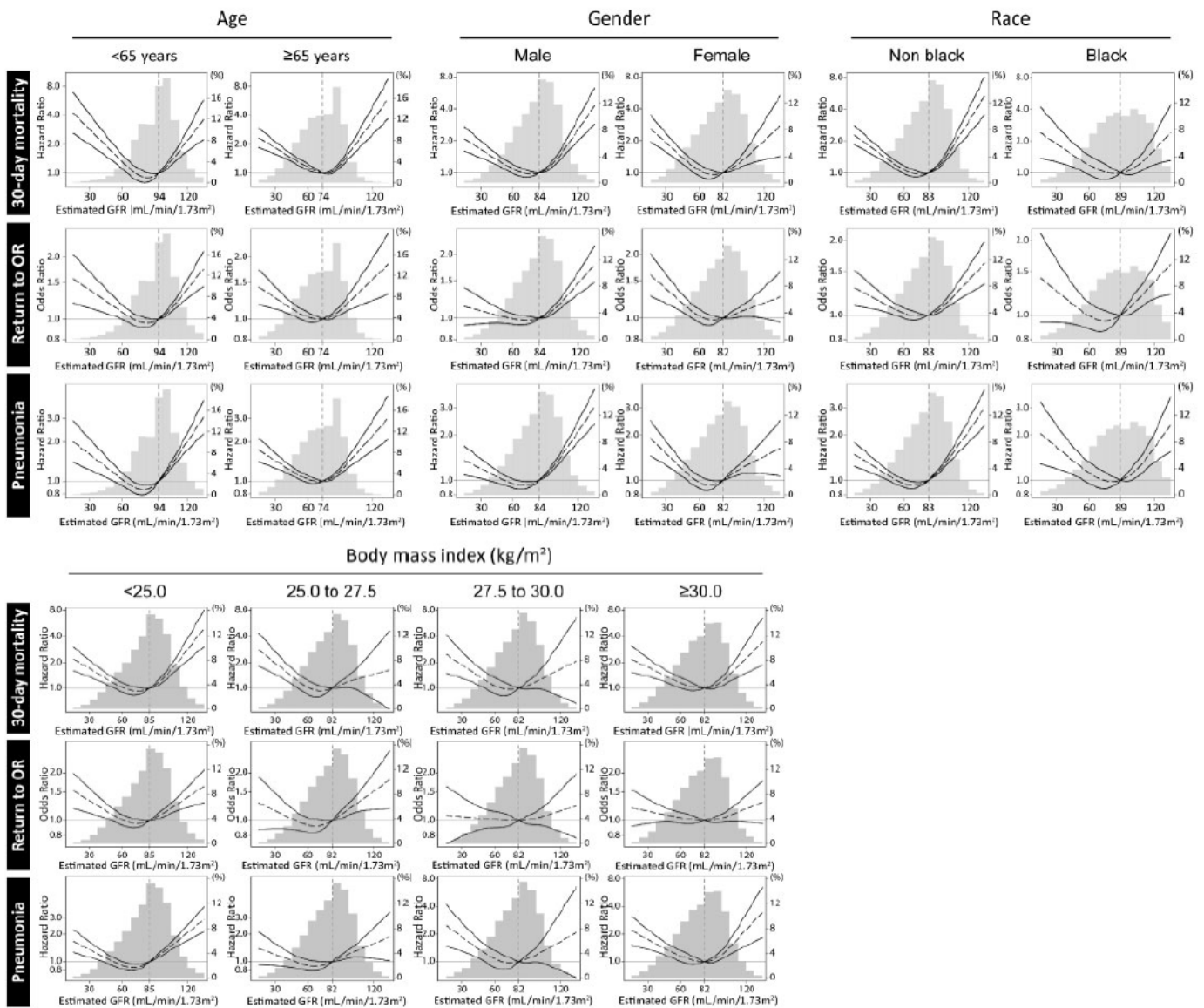


FIGURE 4: Stratified analysis using restricted cubic spline models stratified by age (<65, ≥65 years), gender, race and quartiles of BMI for 30-day mortality, return to the operating room and pneumonia. Lines represent the median of eGFR for each reference group. Cox proportional hazards models with restricted spline function were evaluated for 30-day mortality and pneumonia with adjustments for age, gender, race and diabetes. A logistic regression model was evaluated for return to the operating room with the same adjustment.

on the relative value rather than a fixed absolute value. Our results indicate that we may need to adjust eGFR to include data concerning demographics when assessing the postoperative risk. Supporting this notion, the associations between absolute eGFR values and outcomes were significantly modified by age in our study, but consistently showed a U shape when eGFR was modeled as a continuous variable with spline functions.

Age contributed to the differences in HRs for 30-day mortality between the unadjusted model and the case mix-adjusted model in patients with high eGFR. Age is one of the factors that affects the distribution of eGFR values. The high eGFR group contained more younger patients and fewer older patients [21]. In addition, younger patients (<65 years) had a lower probability of 30-day mortality than older patients (≥65 years). We observed a U-shaped relationship between 30-day mortality and eGFR even though patients with a high eGFR had a lower 30-day postoperative mortality using an unadjusted model.

The type of malignancy also modified the eGFR–outcome association. There are large differences in the incidence of complications according to the type of cancer and the type of surgical resection [3], which may influence the development of other complications. The U-shaped relationship between 30-day mortality and eGFR in patients with esophagus, gastric and colorectal cancer was also observed. This suggests that frailty and

glomerular hyperfiltration contributed to undesired outcomes. However, patients with pancreatic cancer did not demonstrate this same relationship. Surgical outcomes of pancreas surgery largely depend on a variety of postsurgical morbidities (e.g. delayed gastric emptying, pancreatic fistula), which are strongly related to the nature of the surgical procedure. Therefore the impact of renal function may be less than other factors that influence outcomes after surgery for patients with pancreatic cancer [47]. These causes of complications may be due to the interaction of the type of cancer with a high eGFR or may be related to the nature of the surgical resection undertaken for that malignancy. There was no consistent interaction of other variables examined (obesity, diabetes and race) in the subgroup analyses, suggesting that these significant interactions could occur by chance.

This study has several acknowledged limitations. First, because of the nature of an observational study, there may be residual and/or unmeasured confounding factors that could bias the estimated association (e.g. inflammatory markers and socioeconomic factors) [48, 49]. In addition, the ACS-NSQIP database had limited information on the cause of 30-day mortality and the details of cancer stage in these patients. We could not investigate the relationship between disease severity and outcomes, although outcomes may vary depending on the general condition of these patients. Second, errors in creatinine-based eGFR become larger with higher eGFR levels, especially when $>60\text{mL}/\text{min}/1.73\text{m}^2$ [21]. Although the association of high eGFR with outcomes may change if a more accurate cystatin C-based formula is used to calculate eGFR [28], cystatin C is still not widely used in current clinical practice. Third, the ACSNSQIP database had only one measurement of preoperative eGFR and it did not have data on the cause of chronic kidney disease and albuminuria.

In conclusion, among patients undergoing surgery for gastrointestinal malignancies, relatively high eGFR levels, as well as low eGFR levels, are associated with postoperative mortality and morbidity. Awareness of the potential increased risk with a high eGFR at the time of preoperative evaluation may improve surgical outcomes through careful monitoring and preventive measures.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](#).

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The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS-NSQIP are the source 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.

AUTHORS' CONTRIBUTIONS

T.U., Y.O. and A.S. contributed to the conception of the study, conducted the analysis and interpretation data and drafted the manuscript. R.F.A., N.T.N. and K.K.-Z. contributed to the interpretation of data and revised the manuscript critically for important intellectual content. A.K.L., H.S., M.J.S. and H.I. contributed to the acquisition and interpretation of data and revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

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