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ORIGINAL ARTICLE

Early Surgical Intervention for Acute Ulcerative Colitis Is Associated with Improved Postoperative Outcomes

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Abstract

Background Timing of surgical intervention for acute ulcerative colitis has not been fully examined during the modern immunotherapy era. Although early surgical intervention is recommended, historical consensus for "early" ranges widely. The purpose of this study was to evaluate outcomes according to timing of urgent surgery for acute ulcerative colitis.

Methods All non-elective total colectomies in ulcerative colitis patients were identified in the National Inpatient Sample from 2002 to 2014. Procedures, comorbidities, diagnoses, and in-hospital outcomes were collected using International Classification of Disease, 9th Revision codes. An operation was defined as early if within 24 hours of admission. Results were compared between the early versus delayed surgery groups.

Results We found 69,936 patients that were admitted with ulcerative colitis, and 2650 patients that underwent non-elective total colectomy (3.8%). Early intervention was performed in 20.4% of patients who went to surgery. More early operations were performed laparoscopically (28.1% versus 23.3%, $p = 0.021$) and on more comorbid patients (Charlson Index, $p = 0.008$). Median total hospitalization costs were $20,948 with an early operation versus $33,666 with a delayed operation ($p < 0.001$). Delayed operation was an independent risk for a complication (OR = 1.46, $p = 0.001$). Increased hospitalization costs in the delayed surgery group were statistically significantly higher with a reported complication (OR = 3.00, $p < 0.001$) and lengths of stay (OR = 1.26, $p < 0.001$).

Conclusion Delayed operations for acute ulcerative colitis are associated with increased postoperative complications, increased lengths of stay, and increased hospital costs. Further prospective studies could demonstrate that this association leads to improved outcomes with immediate surgical intervention for medically refractory ulcerative colitis.

Keywords Ulcerative colitis · Refractory · Colectomy · Emergency surgery

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Introduction

Admission to the hospital for an acute ulcerative colitis (UC) flare is a critical harbinger of worsening disease and impending need for surgical management. One- and 5-year colectomy rates following such hospitalization are approximately 50 and 70%, respectively.[1] Rates of colectomy during the index hospital admission remain at 10–15% even in the modern biologic era.[2,3]

Once a severe UC flare has been determined to be medically refractory and threatening perforation, aggressive surgical intervention is the mainstay therapy. Since the early years of multidisciplinary approach to UC, early intervention and complete total abdominal colectomy have characterized best practice.[4] Surgeon *gestalt* for early intervention is based on the precept that if a patient is going to require a colectomy, then sustaining one's declining health, malnourishment, and immunosuppression will increase the already high morbidity and mortality risks associated with urgent surgical intervention for UC.[5,6] In addition, pathophysiologic studies have demonstrated an association between the architectural changes of the gastrointestinal lumen, multiorgan dysfunction, and ultimately death.[7,8]

Much of the literature to date has focused on avoiding surgery through the development of new biologic agents and the improvement of acute UC flare protocols.[2,9–11] However, these advances should not eclipse an important but less well-understood question: For patients that will require a same-admission colectomy, is the operative need a matter of days or hours? Although same-admission colectomies for acute UC flares are routinely described as "emergent" protocols, recommendations described in the literature span formal definitions for both surgical emergency and urgency.[6,12] The surgical literature has widely debated how early is sufficient with current consensus recognizing the balancing of preoperative resuscitation with the ongoing physiologic insult of irrecoverable bowel.[12–16]

Given that these same-admission colectomies for UC are often preceded by steroid rescue dosing and close follow-up, we believe that resuscitation needs in this patient population prior to colectomy may be overstated, and the lasting effects of the persistent inflammatory cascade underestimated. The purpose of this study was to determine if UC patients requiring emergency surgery had improved outcomes (e.g., decreased surgical complications, decreased lengths of stay, and decreased costs) when surgery was performed within 24 h versus greater than 24 h.

Materials and Methods

Data Source and Case Identification

We identified all adult patients admitted to hospitals with a diagnosis of UC who ultimately underwent a non-elective total colectomy that same admission from the Agency for Healthcare Research and Quality's Healthcare Utilization Project's National Inpatient Sample (NIS) from January 1, 2002 to December 31, 2014. UC patients were identified using International Classification of Diseases, 9th Revision (ICD-9) diagnosis code 55.6. A total colectomy was identified by ICD-9 procedure codes 45.8, 45.81, 45.82, and 45.83. Laparoscopic cases were identified by those labeled as 45.82. Cases coded as elective were excluded. Due to the comparative approach, NIS US population weights were not necessary and not employed.

NIS Variable Selection

Patients were classified as having an "early" surgical intervention if the procedure day was 24 h or less following admission. All other surgical interventions were classified as "late." Due to the ongoing controversy of the "weekend effect" and how it might limit immediate access to surgical intervention for a patient that was urgent but not emergent,[17–20] we pre-planned a sensitivity analysis allowing for an additional day of inpatient admission prior to surgery for the early intervention when a patient was admitted on the weekend.

We used a consensus-driven selection process between four experienced colorectal surgeons and two experienced gastroenterologists to identify other study variables for further analysis. Patient demographics included sex, race, and age categorized into decades. NIS hospital characteristics were also included. Comorbidities were categorized by organ system and identified using ICD-9 codes previously reported.[21,22] Charlson Comorbidity Index group scores were calculated using previously described methods.[23]

NIS Outcome Variables

In-hospital mortality and postoperative length of stay (LOS) were obtained from the NIS dataset. "Extended" length of stay was defined as postoperative length of stay beyond the 75th percentile. Postoperative complications were identified using ICD-9 codes and categorized by organ system.[21,22] Hospitalization costs per patient in 2013 US dollars were derived using NIS hospital-specific cost-to-charge ratios and annual growth rates provided by the US Bureau of Labor Statistics Consumer Price Index.

Statistical Analysis

The population undergoing early versus late non-elective total colectomies for UC was compared. Continuous variables were compared using Wilcoxon-Mann-Whitney tests of medians. Binary and categorical variables were compared using χ^2 tests of proportions. Logistic regressions were used to examine independent risks of mortality, complication, lengths of stay, and costs. Models were constructed using a priori surgeon and gastroenterologist consensus and further evaluation of univariable tests. Due to the high potential for between-group differences, a secondary regression analysis was performed with a propensity score matched subsample for comparison using 1:1 nearest neighbor matching with replacement. A p value of less than 0.05 was considered statistically significant. All analyses were performed using Stata® 14.2 (StataCorp, College Station, TX). This study design was reviewed and approved by the Johns Hopkins Medicine Institutional Review Board.

Results

UC patients represented 69,936 non-elective hospital visits within the NIS, and 2650 of those patients underwent non-elective total colectomy (3.8%). For those requiring emergency total colectomy, there was a statistically significant difference in the initial open versus laparoscopic approach (early 71.9% versus delayed 76.7%, p = 0.021), grouped Charlson Comorbidity Index (least comorbidities, "0": 68.8% in early group versus 71.8% in late group, p = 0.003), and geographic region (p = 0.005). There was no statistically significant difference between those taken to surgery early versus late for age category, race, pre-existing comorbidities, urban versus rural hospitals, and teaching status of hospitals (Table 1).

Univariable analysis of outcomes (Table 2) demonstrated early operation to be associated with a lower complication rate (44.5 versus 51.6%, p = 0.003) primarily driven by renal dysfunction (8.2 versus 12.9%, p = 0.002), gastrointestinal complaints (4.2 versus 10.0%, p < 0.001), and venous thromboembolic events (3.9 versus 6.3%, p = 0.035). Those operated on early also had reduced rates of total hospital stays (median 8 versus 16 days, p < 0.001) and a trend towards shorter postoperative lengths of stay (p = 0.096). Median total hospitalization costs were $20,948 with an early operation versus $33,666 with a delayed operation (p < 0.001). There was no significant difference in mortality between the two groups.

Table 3 reports the results of multivariable logistic regression of complication rate on early operation, controlling for other significant risk factors. The independent predictors of the risk of a complication were increasing age deciles, income quartile, Charlson Index, and delayed operation (OR 1.46, p = 0.001). Table 4 demonstrates that the increased hospitalization costs were statistically significantly higher with a reported complication (OR 3.00, p < 0.001) and increased hospitalization days (OR 1.26, p < 0.001).

Multivariable regression analysis with a propensity score matched sample yielded qualitatively similar results and is reported in Appendix. The pre-planned sensitivity analysis allowing for additional delay due to the weekend effect also demonstrated no qualitative difference in results (results not shown).

Table 1 Patient demographic and baseline characteristics for total abdominal colectomy in acute ulcerative colitis, 2002–2014 (n = 2650)

Number, (%)	Early surgery (n = 541, (20.4%))	Delayed surgery (n = 2109, (79.6%))	p
Age (years)			0.535
< 40	191 (35.3)	825 (39.1)	
41–50	82 (15.2)	319 (15.1)	
51–60	97 (17.9)	337 (16.0)	
61–70	79 (14.6)	286 (13.6)	
> 71	92 (17.0)	342 (16.2)	
Gender			0.107
Male	310 (57.4)	1129 (53.5)	
Female	230 (42.6)	980 (46.5)	
Race$^{(509)}$			0.257
White	388 (80.2)	1370 (82.7)	
Black	28 (5.8)	113 (6.8)	
Hispanic	39 (8.1)	111 (6.7)	
Asian	NR	14 (0.8)	
Other	23 (4.7)	49 (3.9)	
Surgical approach			0.021
Open	389 (71.9)	1617 (76.7)	
Laparoscopic	152 (28.1)	492 (23.3)	
Comorbidities			
Cardiovascular	25 (4.6)	81 (3.9)	0.423
Respiratory	43 (8.0)	204 (9.8)	0.205
Liver	NR	24 (1.15)	0.945
Renal	14 (2.6)	33 (1.6)	0.112
Diabetes	58 (10.8)	214 (10.2)	0.726
Grouped Charlson Index			0.003
0	371 (68.8)	1499 (71.8)	
1	87 (16.1)	382 (18.3)	
2 or greater	81 (15.0)	208 (10.0)	
Zip code income quart. ($)$^{(292)}$			0.996
1–38,999	99 (19.9)	378 (20.3)	
39,000–47,999	123 (24.7)	452 (24.3)	
48,000–63,999	129 (25.9)	481 (25.9)	
> 64,000	147 (29.5)	549 (29.5)	
Hospital region			0.004
Northeast	111 (20.5)	427 (20.3)	
Midwest	114 (21.1)	560 (26.6)	
South	215 (39.7)	681 (32.3)	
West	101 (18.7)	441 (20.9)	
Hospital location$^{(532)}$			0.527
Rural	26 (6.1)	89 (5.3)	
Urban	404 (94.0)	1599 (94.7)	
Teaching status$^{(532)}$			
Non-teaching	125 (29.1)	544 (32.2)	0.209
Teaching	305 (70.9)	1144 (67.8)	

Missing data: > 1% missing reported as superscript

NR not reportable by NIS rules

Discussion

The purpose of this study was to use existing health services data to demonstrate differences in outcomes between early and delayed operative interventions for UC requiring surgery. Conventional wisdom has recognized the benefits of earlier surgical intervention for acute UC, but early has typically been defined as surgery following a short 7- to 10-day course of pharmacologic rescue therapy.[2,4] In practice, we have had many patients who within a few days of admission are identified as requiring urgent surgery, but there is often much internal debate about the preoperative resuscitation and optimization needs. In addition, patients may require repeat counseling visits over the course of several days in order to emotionally prepare for colectomy often with an ostomy. Although these deliberations are common practice, it is not known if such a measured approach to urgent surgery ultimately harms patients.

Table 2 Postoperative outcomes, compared by early versus delayed total abdominal colectomy in acute ulcerative colitis, 2002–2014 ($n = 2650$)

Outcome, *n* (%)	Early surgery (*n* = 541, (20.4%))	Delayed surgery (*n* = 2109, (79.6%))	*p*
Mortality	26 (4.8)	107 (5.1)	0.796
At least one complication	240 (44.5)	1078 (51.6)	0.003
Specific complication			
Cardiovascular	17 (3.2)	56 (2.7)	0.551
Respiratory	109 (20.2)	406 (19.4)	0.681
Liver	NR	NR	0.646
Renal	44 (8.2)	269 (12.9)	0.003
Gastrointestinal	22 (4.1)	208 (10.0)	< 0.001
Wound healing	104 (19.3)	361 (17.3)	0.275
Sepsis	91 (16.9)	336 (16.1)	0.654
Postoperative hemorrhage	18 (3.3)	90 (4.3)	0.312
VTE/PE	21 (3.9)	131 (6.3)	0.035
Total LOS (median, IQR)	8 (6–12)	16 (11–24)	< 0.001
Postoperative LOS (median, IQR)	8 (6–12)	8 (6–13)	0.096
Extended LOS*	112 (20.9)	422 (23.4)	0.225

VTE venous thromboembolism, *PE* pulmonary embolism, *LOS* length of stay, *NR* not reportable

* Defined as LOS > 75th percentile (> 21 days)

We examined UC patients who underwent non-elective total colectomy and compared those who were operated on within 24 h of admission versus those with a longer surgery-free in-hospital interval. When controlling for other factors, those operated on after 24 h had 46% greater odds of a complication. Even more paradoxical, the morbidity benefit seen in the early intervention group was maintained even though those operated upon early were sicker by Charlson Comorbidity Index scores. Although not independently associated with greater hospitalization costs, the evidence (Table 4) suggests that the increased complications and lengths of stay with delayed operations also explain an over 60% increase in the cost of hospitalization between the early and late interventions. In aggregate, these findings support

Table 3 Multivariable logistic regression of at least one complication on predictors in total abdominal colectomy in acute ulcerative colitis, 2002–2014

Factors	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age (years)				
< 40	Reference		Reference	
41–50	1.39 (1.10–1.76)	0.005	1.63 (1.23–2.16)	0.001
51–60	1.99 (1.58–2.49)	< 0.001	1.95 (1.48–2.56)	< 0.001
61–70	2.86 (2.23–3.67)	< 0.001	2.70 (1.99–3.66)	< 0.001
> 71	3.88 (3.04–4.94)	< 0.001	3.77 (2.75–5.18)	< 0.001
Gender				
Male	Reference		Reference	
Female	1.13 (0.97–1.32)	0.118	1.01 (0.83–1.22)	0.929
Race				
Non-white	Reference		Reference	
White	1.21 (0.97–1.51)	0.090	1.06 (0.82–1.36)	0.647
Zip code income quartile				
First	Reference		Reference	
Second	0.76 (0.60–0.98)	0.032	0.84 (0.63–1.12)	0.225
Third	0.65 (0.51–0.83)	0.001	0.73 (0.55–0.97)	0.028
Fourth	0.75 (0.59–0.95)	0.016	0.82 (0.63–1.08)	0.163
Grouped Charlson Index	1.73 (1.53–1.95)	< 0.001	1.36 (1.17–1.58)	< 0.001
Delayed surgery	1.32 (1.10–1.61)	0.003	1.46 (1.17–1.83)	0.001

Table 4 Multivariable logistic regression of high costs of hospitalization (> 75th percentile = $47,477) on predictors in total abdominal colectomy in acute ulcerative colitis, 2002–2014

Factors	Unadjusted OR (95%)	p	Adjusted OR (95% CI)	p
Age (years)				
< 40	Reference		Reference	
41–50	1.51 (1.07–2.13)	0.018	1.33 (0.71–2.47)	0.370
51–60	2.16 (1.57–2.97)	< 0.001	2.13 (1.20–3.78)	0.009
61–70	2.55 (1.84–3.54)	< 0.001	1.76 (0.96–3.23)	0.068
> 71	3.45 (2.57–4.65)	< 0.001	2.07 (1.15–3.73)	0.016
Gender				
Male	Reference		Reference	
Female	1.01 (0.82–1.25)	0.914	1.01 (0.69–1.48)	0.960
Race				
Non-white	Reference		Reference	
White	0.80 (0.59–1.09)	0.160	0.62 (0.37–1.05)	0.068
Zip code income quartile				
First	Reference		Reference	
Second	1.00 (0.72–1.38)	0.985	1.59 (0.88–2.88)	0.121
Third	0.77 (0.55–1.07)	0.116	1.61 (0.90–2.86)	0.109
Fourth	0.99 (0.72–1.35)	0.925	1.83 (1.05–3.20)	0.034
Grouped Charlson Index	1.72 (1.49–1.98)	< 0.001	1.06 (0.80–1.40)	0.684
At least one complication	8.33 (6.33–11.0)	< 0.001	3.00 (1.94–4.64)	< 0.001
Total LOS	1.25 (1.23–1.28)	< 0.001	1.26 (1.22–1.29)	< 0.001
Delayed surgery	2.57 (1.87–3.53)	< 0.001	0.38 (0.22–0.65)	< 0.001

early surgical intervention for those patients with acute UC who will ultimately require a same-admission total colectomy.

The limitations of this study center primarily on the intrinsic difficulties of the NIS as a retrospective analysis of an administrative dataset. The NIS uses ICD-9 coding for both procedures and diagnoses. Although it may be true that a patient coded as having UC has the disease and that a patient coded as undergoing a targeted procedure was operated upon, the linking of these two facts is a product of our analysis rather than an inherent linkage within the dataset. This limitation may be reflected in the unexpectedly low rate of colectomies among UC admissions reported in our results but should not materially change our overall findings. Second, the NIS does not include data regarding operative indication, so we had to assume causal inference between an individual undergoing an urgent total colectomy who is also diagnosed with UC. Finally, other important clinical data, such as laboratory values (e.g., nutritional labs, anemia, *Clostridium difficile* coinfection), current medication regimen (e.g., steroids, biologics), day-to-day clinical status, and temporality of postoperative events, are not captured by NIS. These limitations ultimately cannot be resolved with the administrative data performed in this exploratory analysis, but the analysis does provide a roadmap for further prospective studies to better study the benefits of immediate surgery.

The second set of limitations acknowledges the limitations of how the findings reported here should be interpreted epidemiologically. This study does not provide further updates of colectomy-free survival, although studies in both the pre-biologic and modern eras have thoroughly addressed this question.[2,3,9] Furthermore, this study is not able to highlight the important transition point when the multidisciplinary care team acknowledges the failure of medical therapy for UC and begins to consider surgical intervention. The NIS provides data on admission and date of surgery, but we are not able to report on the sequence of events (e.g., admission for medical therapy, surgical consultation) that occurs between these two points. While these limitations do prohibit a more in-depth analysis or recommendations based on existing data, other critical surgical decision-making junctures have a similar dearth of high quality data and rely on observational studies and meta-analyses for current professional society guidelines. For example, current practice guidelines for surgical intervention for *C. difficile* colitis are based on a similarly designed study that noted worse outcomes with further delay if surgery was inevitable.[24–26]

Given these limitations, an important final question is where do the findings of this study sit in the literature? Urgent surgical intervention for UC remains a critical episode in the care of chronic UC patients. Although a broad expansion of the pharmacologic arsenal of the last 50 years has radically reduced mortality and the total number of UC flares,[10,11,27–29] overall colectomy rates have remained largely unchanged across the whole population.[2,30–32] The clinical dilemma of when to operate on acutely ill UC persists in the daily practice of the medical and surgical services caring for these patients.

The findings reported here raise concern that in these clinical encounters, a combination of the impaired host physiology and rapidly progressing disease mediators requires urgent operation more than these patients benefit from prolonged resuscitative efforts. The benefits of the diverse medical therapies now widely available and routinely used also may explain why when patients present requiring surgery, further trials of medical therapy are not useful. The increased Charlson Comorbidity Index scores in the early group suggest that those intervened upon earlier were even sicker than the delayed group, which makes their better postoperative outcomes even more surprising. The methods used in this study cannot fully describe the mechanisms of this phenomenon, and a well-designed prospective study is required for these findings to be broadly actionable. However, these findings suggest that refractory acute ulcerative colitis is a surgical emergency and any delay contributes to worse outcomes.

Conclusion

Using a representative US nationwide dataset, UC patients undergoing non-elective total colectomy had higher mortality, higher rates of complication, longer lengths of stay, and more expensive hospitalizations when comparing those operated on immediately versus those operated on after 24 h or more. Prospective studies are needed to affirm causality and identify potential subgroups that would most benefit.

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Compliance with Ethical Standards This study design was reviewed and approved by the Johns Hopkins Medicine Institutional Review Board.

Appendix

We performed propensity score matching described below and repeated a portion of the statistical analysis on high-level findings to confirm that observed differences were not due to limitations of conventional logistic regression analysis. This mirrored analysis is described through the series of complementary tables below. Propensity score assignment and 1:1 nearest neighbor matching with replacement was performed using the teffects package within Stata® 14.2 (StataCorp, College Station, TX). Covariates matched included sex, race, age, income quartile, and Charlson Comorbidity Index group. Patients unable to be matched were excluded from further analysis. A total of 325 patients from the delayed surgery group were individually matched to 539 patients in the early surgery group.

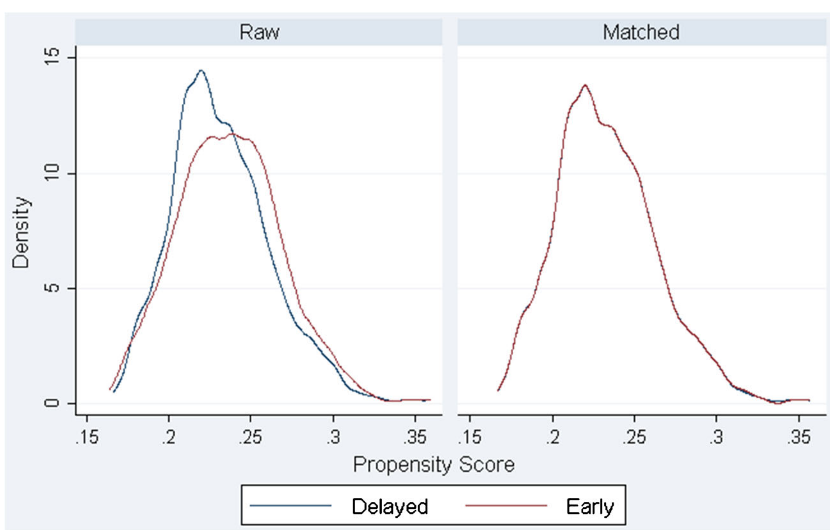

Fig. 1 Distribution of aggregate covariate similarity pre- and postpropensity score matching when modeling in-hospital mortality

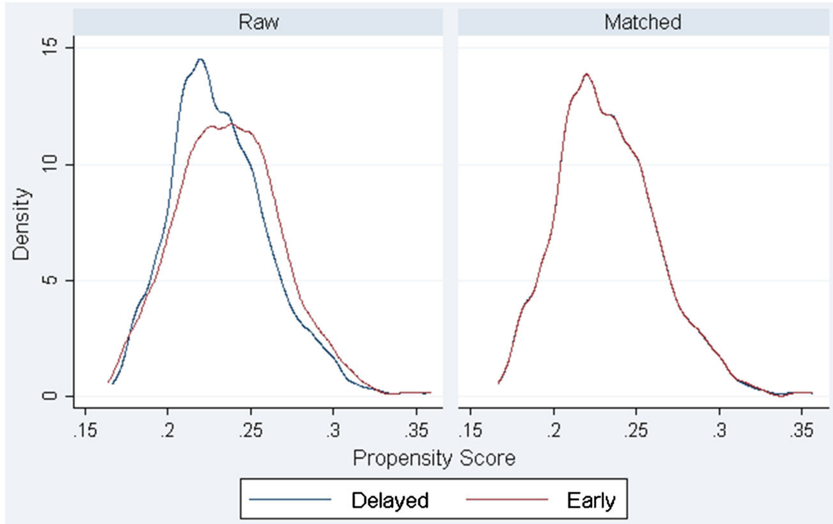

Fig. 2 Distribution of aggregate covariate similarity pre- and postpropensity score matching when modeling the risk of in-hospital complication

Table 5 Patient demographic and baseline characteristics for total colectomies, propensity-weighted sample, 2002–2014 (n = 863)

Number (%)	Early surgery 538 (64.0)	Delayed surgery 325 (35.97)	p
Age (years)			0.886
< 40	191 (35.4)	119 (36.6)	
41–50	82 (15.2)	46 (14.2)	
51–60	97 (18.0)	58 (17.9)	
61–70	78 (17.9)	41 (12.6)	
> 71	91 (16.9)	61 (18.77)	
Gender			0.250
Male	308 (57.3)	173 (53.2)	
Female	230 (42.8)	152 (46.8)	
Race(115)			0.217
White	386 (80.1)	223 (83.8)	
Black	28 (5.8)	18 (6.8)	
Hispanic	39 (8.1)	19 (7.1)	
Asian	NR	NR	
Other	23 (4.6)	NR	
Surgical approach			0.057
Open	388 (72.0)	253 (77.9)	
Laparoscopic	151 (28.0)	72 (22.2)	
Comorbidities			
Cardiovascular	25 (4.6)	17 (5.2)	0.695
Respiratory	43 (8.0)	33 (10.2)	0.274
Liver	NR	NR	0.790
Renal	14 (2.6)	NR	0.173
Diabetes	58 (10.8)	37 (11.4)	0.776
Grouped Charlson Index			0.007
0	230 (70.8)	371 (68.8)	
1	87 (16.1)	68 (20.9)	
2 or greater	81 (15.0)	27 (8.3)	
Zip code income quart. ($)(92)			0.908
1–38,999	98 (19.8)	52 (18.9)	
39,000–47,999	123 (24.8)	74 (26.9)	
48,000–63,999	128 (25.8)	72 (26.2)	
> 64,000	147 (29.6)	77 (28.0)	

Missing data: > 1% missing reported as superscript

NR not reportable by NIS rules

Table 6 Multivariable logistic regression with propensity score matching for in-hospital death and in-hospital complication rate

Factors	Mortality adjusted odds ratio	Morbidity adjusted odds ratio
Age		
< 40	Ref	Ref
41–50	1.85	1.41
51–60	1.82	1.75*
61–70	13.1	2.48**
> 71	18.2	4.12**
Gender		
Male	Ref	Ref
Female	0.89	1.03
Race		
Non-white	Ref	Ref
White	0.54	1.14
Zip code income quartile		
First	Ref	Ref
Second	0.91	0.83
Third	0.57	0.82
Fourth	0.60	0.92
Grouped Charlson Index	0.97	1.37*
Delayed surgery	1.37	1.45*

*$p < 0.05$; **$p < 0.001$

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