



Obesity is Associated with Worse Outcomes Among Abdominal Trauma Patients Undergoing Laparotomy: A Propensity-Matched Nationwide Cohort Study

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Abstract

Introduction Obesity is associated with increased morbidity and mortality in abdominal trauma patients. The characteristics of abdominal trauma patients with poor outcomes related to obesity require evaluation. We hypothesize that obesity is related to increased mortality and length of stay (LOS) among abdominal trauma patients undergoing laparotomies.

Methods Abdominal trauma patients were identified from the National Trauma Data Bank between 2013 and 2015. Patients who received laparotomies were analyzed using propensity score matching (PSM) to evaluate the mortality rate and LOS between obese and non-obese patients. Patients without laparotomies were analyzed as a control group using PSM cohort analysis.

Results A total of 33,798 abdominal trauma patients were evaluated, 10,987 of them received laparotomies. Of these patients, the proportion of obesity in deceased patients was significantly higher when compared to the survivors (33.1% vs. 26.2%, $p < 0.001$). Elevation of one kg/m^2 of body mass index independently resulted in 2.5% increased odds of mortality. After a well-balanced PSM, obese patients undergoing laparotomies had significantly higher mortality rates [3.7% vs. 2.4%, standardized difference (SD) = 0.241], longer hospital LOS (11.1 vs. 9.6 days, SD = 0.135), and longer intensive care unit LOS (3.5 vs. 2.3 days, SD = 0.171) than non-obese patients undergoing laparotomies.

Conclusions Obesity is associated with increased mortality in abdominal trauma patients who received laparotomies versus those who did not. Obesity requires a careful evaluation of alternatives to laparotomy in injured patients.

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Introduction

The prevalence of obesity is rising rapidly in the USA (US) and other industrialized nations. Approximately, one-third of the US adult population is obese [1–3]. It is a public health concern associated with numerous medical problems including diabetes, coronary artery disease, hypertension,

hyperlipidemia, and various types of cancer [4–7]. A high body mass index (BMI) is also associated with postoperative morbidity for patients requiring surgical treatment [8–10].

Previous publications indicate that obesity may increase morbidity and mortality of abdominal trauma patients [11]. Intensive care unit (ICU) admission and mechanical ventilator support are frequently used in the management of abdominal trauma patients and can be markers for poor outcomes in the obese as well [12].

Our study sought to delineate the characteristics of abdominal trauma patients who might have obesity-related adverse outcomes. Although most abdominal trauma patients can be treated non-operatively, some require laparotomies [13, 14]. There is a significant increase in complications, infectious, and surgical, in obese patients following surgical intervention [8–10, 15, 16].

The National Trauma Data Bank (NTDB) serves as the largest databank for traumatic injuries and outcomes in the USA [17]. In this study, a nationwide analysis was performed using the NTDB to evaluate the role of obesity in abdominal trauma patients who required laparotomies. We hypothesize that obese patients undergoing trauma laparotomy have a higher mortality and longer length of stay (LOS) than non-obese patients. This information will help physicians improve care by modifying protocols for managing obese trauma patients and maintaining a higher index of suspicion for poor outcomes.

Methods

Study design and setting

A retrospective cohort analysis of abdominal trauma patients in the NTDB was undertaken for the years 2013–2015. The inclusion criteria were patients with blunt or penetrating abdominal trauma (trauma mechanism: blunt or penetrating, origin file: RDS_ECODE and RDS_ECOCODEDES; ICD-9-CM: 863.xx-869.xx, origin file: RDS_DCODE and RDS_DCODEDES) (Electronic Supplementary Material Table 1). Patients with burns, unknown trauma mechanism, incomplete records, and BMIs less than 15 or greater than 50 were excluded [18]. Patients with abdominal trauma as the dominant injury were the focus of current study. Patients with severe injuries [abbreviate injury scale (AIS) ≥ 3] to other regions, outside of the abdomen, were excluded from the study (Fig. 1) [19].

Data for age, gender (origin file: RDS_DEMO), systolic blood pressure (SBP) in the emergency department (ED), pulse in the ED, respiratory rate (RR) in the ED, Glasgow coma scale (GCS) in the ED (origin file: RDS_ED), blunt or penetrating trauma, transportation time (EMSMINS in origin file: RDS_ED), ED time (EDMINS in origin file: RDS_ED), comorbidities (origin file: RDS_COMORBID), use of transfusion (PCODEs: 99.0–99.09, origin file: RDS_PCODE and RDS_PCODEDES), laparotomies (Electronic Supplementary Material Table 2), injury severity score (ISS), and body mass index (BMI) [body weight (kg)/body height (m)²] were collected and evaluated. Obesity was defined as BMI over 30 kg/m² [20]. Mortality, hospital LOS, and ICU LOS (origin file: RDS_DISCHARGE) were designated as outcomes. Patients who were coded as deceased/expired in the column HOSDISP (hospital disposition) were defined as such (origin file: RDS_DISCHARGE). As per the NTDB, comorbidities were defined as alcohol use disorder, bleeding disorder, currently receiving chemotherapy for cancer, congenital anomalies, congestive heart failure, current smoker, chronic renal failure, cerebrovascular accident, diabetes mellitus, disseminated cancer, advanced directive limiting care, functionally dependent health status, history of angina within 30 days, history of myocardial infarction, history of peripheral vascular disease, hypertension requiring medication, prematurity, chronic obstructive pulmonary disease, steroid use, cirrhosis, dementia, major psychiatric illness, drug use disorder, attention deficit disorder/attention deficit hyperactivity disorder, and other [21].

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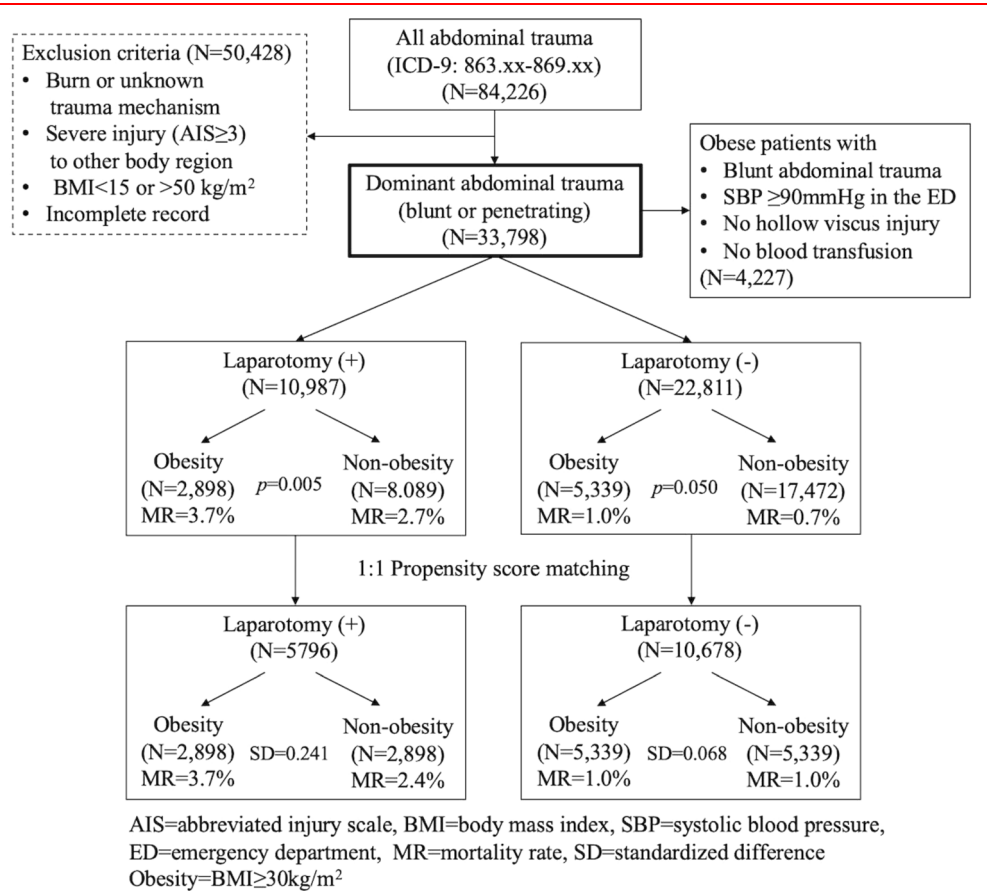
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Fig. 1 Study population and protocol of current study

Statistical analysis

Survivors and non-survivors of abdominal trauma patients who underwent laparotomies were compared (Table 1). Nominal data are presented as a percentage with a 95% confidence interval (CI) and were compared using Chi-square test, and numerical data are presented as the mean with 95% CI and were compared using the Mann–Whitney *U* test. (ISS was presented as the median and interquartile range.) A value of $p < 0.05$ was considered statistically significant. Statistically significant variables in the bivariate analysis were put into a multivariate logistic regression (MLR) model using the “enter method” (gray area of Table 1). CI not including or crossing 1.000 was considered statistically significant. Due to multicollinearity between BMI and obesity, only BMI was included in the regression model. Independent risk factors and the associated odds ratios for mortality of abdominal trauma patients who underwent laparotomies were analyzed accordingly.

We used two analytic approaches to evaluate the effect of obesity on outcomes for abdominal trauma patients who did and did not receive a laparotomy. First, a one-to-one propensity score matching (PSM) methodology was used to minimize selection bias between patients with laparotomies

who were obese and non-obese, and constructed pairs of obese patients and non-obese patients with the greedy neighbor approach. A caliper setting of 0.1 was utilized [22]. Standardized differences (SD) were used to confirm a balanced matching result. The matching result was considered balanced when SD was less than 0.1 (Fig. 1, Table 2) [23]. After a well-balanced matching, outcomes between obese and non-obese patients were compared (Table 3). A similar PSM was performed in obese and non-obese patients without laparotomies as a control.

Second, an adjusted MLR model was performed to evaluate the effect of obesity on mortality for patients with laparotomies. Patients without laparotomies were also analyzed using this model as a control group (Table 4). Covariables which may have affected trauma outcomes clinically were considered for PSM and adjusted in the MLR model. These covariables included age, gender (male sex), SBP, pulse, RR, GCS, trauma mechanism (penetrating trauma), transportation time, ED time, comorbidities, use of transfusion, and ISS.

All original files of NTDB were merged and analyzed with R software, version 3.5.0 of R Core Team (R Foundation for Statistical Computing, Vienna, Austria, 2018) and R Studio software, version 1.1.453 of R Studio:

Table 1 Comparisons of characteristics between non-survivors and survivors and independent risk factors for mortality (multivariate logistic regression) in abdominal trauma patients who received laparotomy ($N = 10,987$)

	Bivariate analysis			Multivariate logistic regression
	Non-survivors ($N = 323$)	Survivors ($N = 10,664$)	p value	Odds of mortality [‡] (95% CI)
Age (years)	44.4 (44.1–47.7)	34.2 (33.9–34.5)	<0.001*	1.029 (1.021–1.036)
Male (%)	80.8 (76.5–85.1)	79.5 (79.0–80.6)	0.564 [†]	–
SBP in ED (mmHg)	92.4 (86.7–98.1)	125.5 (124.9–126.1)	<0.001*	0.987 (0.984–0.990)
Pulse in ED (/min)	91.5 (86.7–96.3)	93.5 (93.0–93.9)	0.029*	1.005 (1.001–1.009)
RR in ED (/min)	16.7 (15.4–17.7)	19.4 (19.2–19.5)	<0.001*	0.999 (0.983–1.016)
GCS in ED	9.0 (9.0–10.2)	14.1 (14.0–14.1)	<0.001*	0.897 (0.860–0.898)
Penetrating (%)	54.5 (49.1–59.9)	61.5 (60.6–62.4)	0.011 [†]	1.230 (0.938–1.613)
Transportation time (min)	172.5 (127.7–217.3)	249.0 (237.4–260.6)	0.780*	–
ED time (min)	79.4 (64.8–94.0)	114.7 (110.6–118.7)	<0.001*	0.999 (0.999–1.000)
Comorbidity (%)	52.3 (46.9–57.7)	54.9 (54.0–55.8)	0.353 [†]	–
Use of transfusion (%)	61.9 (56.6–67.2)	24.0 (23.2–24.8)	<0.001 [†]	2.248 (1.742–2.901)
ISS	16 (15)	9 (9)	<0.001*	1.086 (1.070–1.102)
BMI	28.4 (27.7–29.2)	26.9 (26.8–27.1)	<0.001*	1.025 (1.005–1.045)
Obesity (%)	33.1 (28.0–38.2)	26.2 (25.4–27.0)	0.005 [†]	–

Numerical data: mean (95% CI: lower–upper) (ISS was presented as the median and interquartile range)

Nominal data: percentage (95% CI: lower–upper)

*Mann–Whitney U test, [†]Chi-square test, [‡]Multivariate logistic regression (CI not including or crossing 1.000 was considered statistically significant)

SBP systolic blood pressure, ED emergency department, RR respiratory rate, GCS Glasgow coma scale, ISS injury severity score, BMI body mass index, CI confidence interval

Integrated Development for R (R Studio, Inc., Boston, Massachusetts, 2016) [24].

Results

Characteristics of study subjects

During the 3-year study period, there were 84,226 abdominal trauma patients (ICD-9: 863.xx-869.xx) in the NTDB. A total of 33,798 patients (Blunt trauma: 75.4%, $N = 25,473$; penetrating trauma: 24.6%, $N = 8325$) were studied with a mean BMI of 26.5. 10,987 patients (32.5%) received laparotomies (Fig. 1). In patients who underwent laparotomies, non-survivors had a significantly higher BMI (28.4 vs. 26.9, $p < 0.001$), higher proportion of obesity (33.1% vs. 26.2%, $p = 0.005$). The MLR analysis showed that BMI serves as an independent factor of mortality after adjusting for age, SBP, pulse, RR, GCS, trauma mechanism (penetrating trauma), ED time, use of transfusion, and ISS. Each unit increase in BMI increases the odds of mortality by 2.5% (odds ratio = 1.025, 95% CI: 1.005–1.045) (Table 1).

Effects of obesity on outcomes in patients who received laparotomies or not were evaluated using PSM and MLR chorot analysis.

The relationship between mortality and BMI in patients who received laparotomies or not is depicted in Fig. 2. A comparison of slopes between these two groups [R^2 of laparotomy (+) = 0.9144, R^2 of laparotomy (–) = 0.8383] demonstrates that the mortality significantly increased as BMI increased among patients receiving a laparotomy [estimated marginal means of laparotomy (+): 2.953 (2.335–3.570), estimated marginal means of laparotomy (–): 1.984 (1.366–2.601), $p < 0.001$, analysis of covariance (ANCOVA)].

PSM yielded well-balanced cohorts of 5796 patients with laparotomies from 10,987 patients (2898 obese patients and 2898 non-obese patients) and 10,678 patients without laparotomy from 22,811 patients (5339 obese patients and 5339 non-obese patients) (Table 2). In patients who received laparotomies, the obese had a higher mortality rate (3.7% vs. 2.4%, SD = 0.241), longer hospital LOS (11.1 vs. 9.6 days, SD = 0.135), and longer ICU LOS (3.5 vs. 2.3 days, SD = 0.171) than the non-obese after matching. However, there was no significant difference in mortality rate, hospital LOS, or ICU LOS between the

Table 2 Characteristics of patients who received laparotomies or not

Laparotomy (+) (<i>N</i> = 10,987)	Pre-propensity matching			Post-propensity matching		
	Obese patients (<i>N</i> = 2898)	Non-obese patients (<i>N</i> = 8089)	SD*	Obese patients (<i>N</i> = 2898)	Non-obese patients (<i>N</i> = 2898)	SD
Age (years)	38.9 (38.3–39.5)	32.9 (32.5–33.3)	0.353	38.9 (38.3–39.5)	37.8 (37.2–38.5)	0.064
Male (%)	79.0 (77.5–80.5)	79.7 (78.8–80.6)	0.027	79.0 (77.5–80.5)	80.2 (78.7–81.7)	0.041
SBP in ED (mmHg)	127.1 (125.9–128.3)	123.6 (122.9–124.3)	0.110	127.1 (125.9–128.3)	127.5 (126.5–128.6)	0.015
Pulse in ED (/min)	95.1 (94.3–96.0)	92.8 (92.3–93.4)	0.093	95.1 (94.3–96.0)	95.5 (94.7–96.3)	0.017
RR in ED (min)	19.4 (19.2–19.7)	19.2 (19.1–19.4)	0.031	19.4 (19.2–19.7)	19.3 (19.1–19.6)	0.013
GCS in ED	13.9 (13.8–14.0)	14.0 (13.9–14.0)	0.009	13.9 (13.8–14.0)	14.0 (13.8–14.1)	0.010
Penetrating (%)	65.9 (64.2–67.6)	59.6 (58.5–60.7)	0.151	65.9 (64.2–67.6)	66.4 (64.7–68.1)	0.012
Transportation time (min)	241.7 (221.2–262.2)	248.6 (235.0–262.1)	0.011	241.7 (221.2–262.2)	246.7 (223.8–269.6)	0.008
ED time (min)	107.8 (100.8–114.8)	115.7 (111.0–120.5)	0.038	107.8 (100.8–114.8)	104.0 (97.5–110.4)	0.021
Comorbidity (%)	62.9 (61.1–64.7)	52.0 (50.9–53.1)	0.247	62.9 (61.1–64.7)	62.8 (61.0–64.6)	0.001
Use of transfusion (%)	27.3 (25.7–28.9)	24.4 (23.5–25.3)	0.082	27.3 (25.7–28.9)	27.8 (26.2–29.4)	0.015
ISS	9 (9)	9 (9)	0.042	9 (9)	9 (9)	0.002
Laparotomy (–) (<i>N</i> = 22,811)	Pre-propensity matching			Post-propensity matching		
	Obese patients (<i>N</i> = 5339)	Non-obese patients (<i>N</i> = 17,472)	SD	Obese patients (<i>N</i> = 5339)	Non-obese patients (<i>N</i> = 5339)	SD
Age (years)	44.1 (43.5–44.7)	31.1 (32.7–33.5)	0.432	44.1 (43.5–44.7)	42.8 (42.2–43.4)	0.031
Male (%)	64.1 (62.8–65.4)	66.3 (65.6–67.0)	0.052	64.1 (62.8–65.4)	65.4 (64.1–66.7)	0.031
SBP in ED (mmHg)	132.6 (131.8–133.4)	127.0 (126.6–127.4)	0.199	132.6 (131.8–133.4)	131.7 (131.0–132.4)	0.030
Pulse in ED (/min)	88.9 (89.0–90.1)	88.1 (87.8–88.5)	0.064	88.9 (89.0–90.1)	89.4 (88.9–90.0)	0.005
RR in ED (min)	18.5 (18.3–18.6)	18.5 (18.4–18.6)	0.008	18.5 (18.3–18.6)	18.3 (18.1–18.4)	0.037
GCS in ED	14.1 (14.0–14.2)	14.1 (14.1–14.2)	0.003	14.1 (14.0–14.2)	14.2 (14.1–14.3)	0.034
Penetrating (%)	7.2 (6.5–7.9)	6.9 (6.3–7.3)	0.020	7.2 (6.5–7.9)	8.3 (7.6–9.0)	0.088
Transportation time (min)	315.8 (295.5–336.2)	302.4 (291.7–313.1)	0.018	315.8 (295.5–336.2)	308.9 (289.7–328.1)	0.009
ED time (min)	309.2 (299.7–318.6)	287.2 (282.6–291.8)	0.068	309.2 (299.7–318.6)	293.7 (285.4–302.1)	0.046
Comorbidity (%)	64.3 (63.0–65.6)	46.2 (45.5–46.9)	0.409	64.3 (63.0–65.6)	64.5 (63.2–65.8)	0.005
Use of transfusion (%)	10.4 (9.6–11.2)	7.9 (7.5–8.3)	0.168	10.4 (9.6–11.2)	10.7 (9.9–11.5)	0.015
ISS	9 (6)	9 (7)	0.058	9 (6)	9 (6)	0.021

Both pre-propensity matching and post-propensity matching between obese patients and non-obese patients are revealed

Numerical data: mean (95% CI: lower–upper) (ISS was presented as the median and interquartile range)

Nominal data: percentage (95% CI: lower–upper)

*SD = standardized difference (SD \geq 0.1 represent significant differences in covariables between groups)

SBP systolic blood pressure, RR respiratory rate, GCS Glasgow coma scale, ED emergency department, ISS injury severity score

obese and non-obese in patients who did not receive laparotomy after matching (Table 3).

In addition to PSM, a MLR analysis showed that in 10,987 patients who received laparotomies, obesity serves as an independent factor to mortality (odds ratio: 1.317, 95% CI: 1.013–1.712, $p = 0.040$) after adjusting for age, gender (male), SBP, pulse, RR, GCS, trauma mechanism

(penetrating trauma), transportation time, ED time, comorbidity, use of transfusion, and ISS (Table 4). A similar adjusted regression model was also performed in patients who did not receive a laparotomy ($N = 22,811$) as a control group. Obesity did not affect mortality significantly in patients who did not undergo a laparotomy (Table 4).

Table 3 Comparisons of outcomes between obese and non-obese patients after propensity score matching

	Laparotomy (+) (<i>N</i> = 5796)		SD*
	Obese patients (<i>N</i> = 2898)	Non-obese patients (<i>N</i> = 2898)	
Hospital LOS (day)	11.1 (10.6–11.6)	9.6 (9.3–9.9)	0.135
ICU LOS (day)	3.5 (3.2–3.8)	2.3 (2.1–2.5)	0.171
Mortality (%)	3.7 (3.0–4.4)	2.4 (1.8–3.0)	0.241
	Laparotomy (–) (<i>N</i> = 10,678)		SD
	Obese patients (<i>N</i> = 5339)	Non-obese patients (<i>N</i> = 5339)	
Hospital LOS (day)	4.9 (4.7–5.0)	4.7 (4.5–4.8)	0.031
ICU LOS (day)	0.8 (0.7–0.8)	0.7 (0.7–0.8)	0.003
Mortality (%)	1.0 (0.7–1.3)	1.1 (0.8–1.4)	0.068

Both patients who received laparotomies or not are revealed

Numerical data: mean (95% CI: lower–upper)

Nominal data: percentage (95% CI: lower–upper)

*SD = standardized difference (SD \geq 0.1 represent significant differences in covariables between groups)

LOS length of stay, ICU intensive care unit

Discussion

Obesity (BMI \geq 30 kg/m²) is associated with numerous morbidities, and appropriate management of obese trauma patients is increasingly essential due to its increasing prevalence [11, 12, 25]. Our current study shows that among abdominal trauma patients, increased BMI is an independent risk factor for mortality.

Complications of abdominal surgical incisions may include hemorrhage, infection, or wound dehiscence [26]. Patients undergoing a laparotomy may suffer a pulmonary embolism, deep vein thrombosis, secondary pneumonia, urinary retention, or a reaction to anesthesia [27, 28]. Among patients requiring surgical intervention, obesity is a significant risk factor for surgical wound infections, increased surgical blood loss, and an increased operative time [8–10, 15, 16]. Surgical complications as well as mortality may be increased in obese patients. Therefore, the deleterious role of obesity seems magnified in patients subjected to surgical stress. In obese trauma patients who receive operations, several complications are reported including pneumothorax or hemothorax related to central catheter placement, surgical site infection, surgical wound dehiscence, failure of surgical anastomoses, and increased ventilator days. It is reasonable to assume that more obese individuals have more complications and the cumulative effect of increased complications in operative intervention leads to increased mortality [29].

Many patients can be treated non-operatively with advanced resuscitation, intensive care, and interventional radiology in the management of abdominal trauma. The patients usually receive close observation with fluid resuscitation or angioembolization [13, 14]. Safe modification of blunt abdominal trauma protocols with a focus on non-operative management in obese patients may avoid significant complications [30].

Postoperative care is important for trauma patients [31, 32]. Obesity is a major risk factor for a number of chronic diseases, complications, and poor outcomes after surgery. Obese patients are difficult to liberate from ventilators and are predisposed to respiratory complications [33]. The treatment of ventilator-associated pneumonia or other infections is more complicated among the obese due to immune system dysregulation, decreased cell-mediated immune responses, and other reported possible mechanisms [34].

Total LOS and days in the ICU might be prolonged due to obesity [31, 32]. The current study demonstrates that obesity is associated with a longer hospital and ICU LOS if the patients undergo laparotomies. This was not demonstrated in obese patients who did not receive laparotomies. A closer observation, aggressive resuscitation, and multidisciplinary treatment for associated comorbidities should be considered in the postoperative care of obese patients.

Our study has several limitations. The NTDB data are retrospective, not complete, and can be inaccurate. We restricted our records to patients with BMI 15–50 kg/m².

Table 4 Multivariate logistic regression analysis for evaluation of independent risk factors for mortality in patients with laparotomy. (Patients without laparotomy were also analyzed as a control group.)

Variables	<i>p</i> value*	Odds of mortality	95% CI	
			Lower	Upper
Laparotomy (+) (<i>N</i> = 10,987)				
Age	<0.001	1.034	1.027	1.042
Male	0.028	1.433	1.041	1.973
SBP in ED (mmHg)	<0.001	0.987	0.984	0.990
Pulse in ED (/min)	0.006	1.006	1.002	1.010
RR in ED (/min)	0.801	0.998	0.982	1.014
GCS in ED	<0.001	0.879	0.860	0.899
Penetrating	0.512	1.098	0.830	1.453
Transportation time (min)	0.007	1.000	0.999	1.000
ED time (min)	0.200	0.999	0.999	1.000
ISS	<0.001	1.087	1.070	1.103
Comorbidity	<0.001	0.572	0.441	0.740
Use of transfusion	<0.001	2.347	1.815	3.036
Obesity	0.040	1.317	1.013	1.712
Constant	<0.001	–	–	–
Laparotomy (–) (<i>N</i> = 22,811)				
Age	<0.001	1.038	1.030	1.047
Male	0.176	1.254	0.904	1.739
SBP in ED (mmHg)	<0.001	0.991	0.987	0.996
Pulse in ED (/min)	0.020	1.007	1.001	1.013
RR in ED (/min)	0.554	1.007	0.983	1.032
GCS in ED	<0.001	0.909	0.885	0.933
Penetrating	<0.001	2.872	1.780	4.632
Transportation time (min)	0.839	1.000	1.000	1.000
ED time (min)	0.973	1.000	1.000	1.000
ISS	<0.001	1.065	1.044	1.086
Comorbidity	0.019	1.566	1.077	2.276
Use of transfusion	<0.001	3.848	2.782	5.322
Obesity	0.831	1.037	0.746	1.441
Constant	<0.001	–	–	–

*Multivariate logistic regression

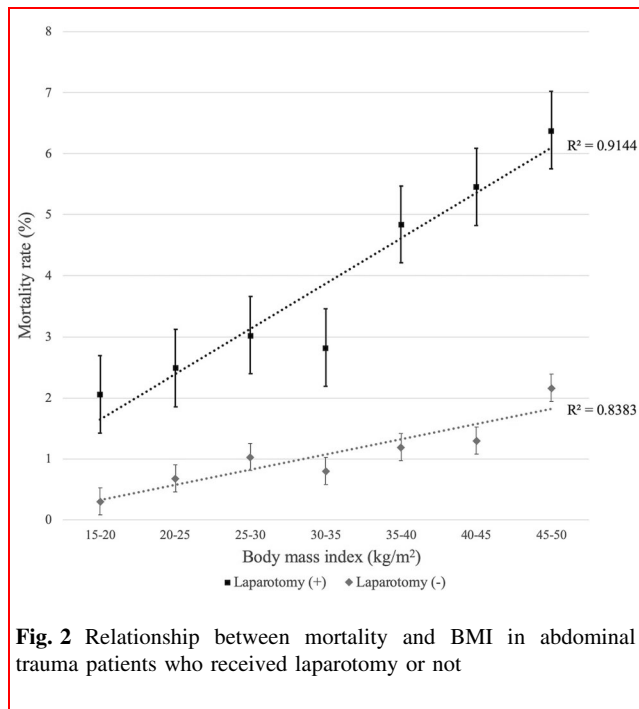
SBP systolic blood pressure, ED emergency department, RR respiratory rate, GCS Glasgow coma scale, ISS injury severity score, CI confidence interval

Patients outside this range are rare [18]. Possible inaccuracies of procedure codes for abdominal operations also limit our conclusions. The aforementioned limitations notwithstanding the results depict important information about the role of obesity in the surgical outcomes of abdominal trauma patients. Further studies with prospective design and long-term follow-ups are needed. The effect of obesity to outcomes of abdominal trauma patients

who received minimal invasive surgery also needs to be evaluated in future studies.

Conclusion

Obesity is associated with increased mortality and LOS in abdominal trauma patients who received laparotomies versus those who did not. A prudent approach to the



decision to perform a laparotomy on obese patients is required.

Author contributions FB, C-YF, and FB were involved in the study conception and design. C-YF was involved in acquisition of data. FB, C-YF, FB, MB, FS, TM, MK, LCT, AD, VS, JM, and SP performed the analysis and interpretation of data. C-YF and RT drafted the manuscript. FB and FB performed the critical revision.

Compliance with ethical standards

Conflict of interest The authors have no commercial associations or sources of support from any grant, funding source, or commercial interest including pharmaceutical or device companies that might pose a conflict of interest.

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