

Body mass index is not associated with reoperation rates in patients with a surgically treated perforated peptic ulcer

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ABSTRACT

INTRODUCTION: The aim of the present nationwide Danish cohort study was to examine the association between body mass index (BMI) and reoperation in patients who are surgically treated for perforated peptic ulcer (PPU).

METHODS: This was a nationwide cohort study of all Danish patients who were surgically treated for benign gastric or duodenal PPU between 2011 and 2013. Outcome measures: Reoperation within 30 days of the primary surgical procedure and 90-day survival. The association between BMI and reoperation are presented as crude and adjusted odds ratios (OR) with 95% confidence intervals (CIs).

RESULTS: A total of 726 patients were included. The median age was 69.5 years (range: 18.2-101.7 years), 51.4% were women (n = 373), 78.4% (n = 569) of the patients had at least one co-existing disease, and 47.5% (n = 345) were categorised as American Society of Anesthesiologists (ASA) class ≥ 3 . Re-operative surgery was done in 124 patients (17.1%). No statistically significant adjusted association between underweight, overweight or obesity and re-operation was found (adjusted OR (95%CI): 0.456 (0.181-1.148), 1.468 (0.857-2.517), and 1.314 (0.663-2.601), respectively. Patients undergoing reoperative surgery had a statistically significantly lower crude 90-day survival than patients without need of reoperative surgery; 63.9% (83/124) versus 75.9% (457/602), $p = 0.037$.

CONCLUSION: In the present nationwide cohort study of PPU patients, no statistically significantly adjusted correlation between BMI and re-operation rates was found. Patients undergoing reoperative surgery had a decreased 90-day survival.

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Perforated peptic ulcer (PPU) is a surgical emergency with mortality rates reaching 25-30% [1]. Perforation of the gastro-intestinal wall by erosion from a peptic ulcer leads to acute peritonitis, and sepsis is believed to account for 40-50% of fatalities [1, 2]. Reoperation following surgery for PPU is associated with adverse outcome [3, 4]. Timely and adequate identification of PPU patients at increased risk of reoperative surgery and adverse outcome is important, as this will enable a thor-

ough and adequate planning of the pre-, intra-, and post-operative phases [4, 5].

A large number of prognostic factors for morbidity and mortality following PPU have been characterised [3]. An abnormal body mass index (BMI) is a predictor of mortality in the general population [6], and obesity is considered a prognostic factor for poor outcome and re-operative surgery in a variety of surgical areas [7-9].

The association between an abnormal BMI and re-operation has not been explored in detail in patients who were surgically treated for PPU. Consequently, the aim of the present nationwide cohort study was to examine the association between BMI and reoperation in patients who were surgically treated for PPU. We hypothesised that obesity could be associated with an increased risk of reoperative surgery in PPU [8-10].

METHODS

Design and approval

This nationwide cohort with consecutive inclusion and prospective data collection was approved by The Danish Data Protection Agency (no. 2013-41-1780) and did not require informed patient consent according to Danish health law. The manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [11].

Study population

All patients surgically treated for benign gastric or duodenal PPU in all hospitals caring for patients with PPU in Denmark between 1 September 2011 and 31 August 2013 were included. Non-surgically treated patients and patients with malignant ulcers were not included. No age restriction was used.

The Danish Clinical Register of Emergency Surgery

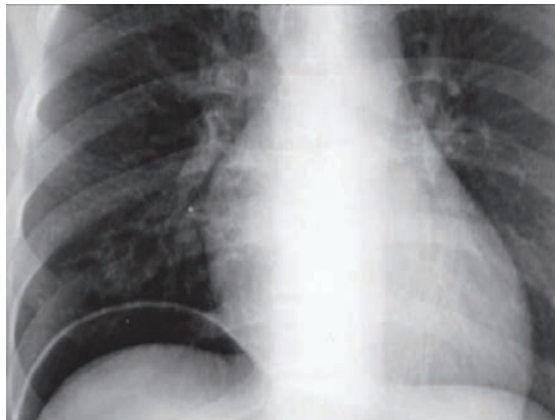
PPU patients were identified using computerised data from the Danish Clinical Register of Emergency Surgery (DCRES) [1]. The DCRES was founded in 2003 by the Danish public health-care authorities. The aim of the DCRES is to monitor the quality of care provided by Danish public hospitals to patients with complicated peptic ulcer disease, through the registration of quality standards, in-

ORIGINAL ARTICLE

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Chest X-ray of a patient with a perforated peptic ulcer. Free gas is clearly visible under the diaphragm.



dicators and prognostic factors. Reporting to the database is mandatory for all Danish hospitals. The Danish National Health Service provides tax-funded health care with free access to hospital-based and primary medical care. Because emergency services, including the treatment of PPU, are provided by the public health-care system only, all patients surgically treated for PPU in Denmark are prospectively reported to the DCRES database. The DCRES database includes baseline characteristics as well as relevant information about the pre-, intra-, and post-operative phases.

Data extraction and management

The following baseline and clinical data were registered: age; sex; co-existing diseases (chronic obstructive pulmonary disease, diabetes, heart disease, liver cirrhosis, malignancy or AIDS, and other chronic conditions); use of medication (aspirin, non-steroidal anti-inflammatory drugs (NSAID), selective serotonin reuptake inhibitors (SSRI), steroids and anticoagulants); lifestyle habits (alcohol abuse; daily use of tobacco); American Society of Anesthesiologists (ASA) grade (I-V); BMI; surgical delay exceeding 6 hours (time from admission to surgery); ulcer site (duodenal/gastric); surgical approach (open, laparoscopic, or laparoscopy converted to open surgery); reoperative surgery (deep infection requiring drainage, wound dehiscence, re-perforation or other type); and 90-day survival. The primary data were recorded by the surgeon using a standard case report form. Data were subsequently validated and transferred to a web-based database by the local DCRES representative at each site. The exact date of death was ascertained through linkage of the patient's civil registration number with the Danish Civil Registry System, which stores information on citizens' vital statistics, including the exact date of death on all Danish citizens [12].

Definition of body mass index

BMI was defined according to World Health Organiza-

tion (WHO) criteria: Patients were classified as underweight (BMI < 18.50 kg/m²), normal weight (BMI: 18.50-24.99 kg/m²), overweight (BMI: 25.00-29.99 kg/m²) or obese (BMI ≥ 30.00 kg/m²).

Outcome measures

The primary outcome measure was reoperation within 30 days of the primary surgical procedure. The secondary outcome measure was 90-day survival.

Statistical analysis

Data were analysed using the SPSS version 20.0 (SPSS, Chicago, Illinois, USA) statistical software package. Baseline and clinical characteristics are presented as distribution frequencies among all patients with PPU in Denmark from 1 September 2011 to 31 August 2013, and stratified according to the primary outcome measure. Binary logistic regression analysis was used to examine the crude and adjusted association between the primary outcome measure and BMI. To present the most conservative estimate, inclusion of known prognostic covariates was done in a single step/block (enter modelling). The regression model was validated using goodness-of-fit tests and model diagnostics, and showed no indication of lack of fit. Results are presented as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI). Adjustment was made for the following prognostic dichotomous co-variables: age over 65 years (y/n), comorbidity (y/n), surgical delay exceeding 6 hours (y/n), and ASA grade 3–5 (y/n) [3].

Finally, the crude association between re-operative surgery and survival was evaluated by survival statistics.

Baseline and clinical characteristics were missing for fewer than 5% of the patients. The prevalence and pattern of missing values in the patient cohort were evaluated, and the data were found not to be missing completely at random (MCAR). Consequently, multiple imputation for the missing values was performed [13].

With a binary response variable, five covariates, $\beta = 0.80$, $\alpha = 0.05$, and an anticipated small effect size, 643 patients were required in order to detect an association between the variables and the primary endpoint [14]. All tests were two-sided and $p < 0.050$ was considered statistically significant.

Trial registration: not relevant.

RESULTS

A total of 726 patients were included. The median age was 69.5 years (range 18.2-101.7 years), 373 (51.4%) were women, and 61.7% of the patients were 65 years or older. Some 569 (78.4%) patients had at least one co-existing disease, and 345 (47.5%) had an ASA score of 3-5. Surgical delay above 6 hours was reported in 371

(51.1%) of the cases (**Table 1**). A total of 310 (42.7%) of the operations were done as open surgery, 238 patients (32.8%) were treated laparoscopically, and 178 (24.5%) of the cases were converted from laparoscopy into laparotomy. Re-operative surgery was done in 124 patients in total (17.1%).

Overall, 51.1% (371/726) of the study population was categorised as being of normal weight; 11.2% (81/726) were underweight; 24.5% (178/726) were overweight; and 13.2% (96/726) were obese. In the binary logistic regression model, a statistically significant crude association between overweight and re-operative surgery was found; OR = 1.690 (95% CI: 1.003-2.845). However, in the adjusted model, this association was no longer statistically significant; OR = 1.468 (95% CI: 0.857-2.517). No statistically significant crude or adjusted associations between underweight or obesity and re-operation were found (**Table 2**).

The overall 90-day survival was 74.4%. Patients undergoing reoperative surgery had a statistically signifi-

cantly lower crude 90-day survival than patients without need for reoperative surgery: 63.9% (83/124) versus 75.9% (457/602), log-rank test $p = 0.048$ (**Figure 1**).

DISCUSSION

In the present nationwide cohort study of patients who were surgically treated for PPU between 2011 and 2013, neither underweight, nor overweight or obesity was associated with an adjusted increased risk of reoperative surgery within 30 days. Reoperation was associated with a decreased crude 90-day survival.

The strengths of the present study include the nationwide population-based design, the complete follow-up for ascertainment of survival and reoperative surgery, and the adjustment for known potential confounders. Participation in the DCRES is mandatory for all departments in Denmark that care for patients with emergency disorders, including PPU, and extensive efforts are made to ensure the validity of data [1, 15]. Some patient records had missing data; however, we performed mul-



TABLE 1

Variable	Total, n (%) (N = 726)	Re-operation, n (%) (N = 124)	No re-operation, n (%) (N = 602)	p-value ^a	Missing, n (%)
Age > 65 yrs	448 (61.7)	82 (66.1)	366 (60.8)	0.266	0 (0.0)
Female gender	373 (51.4)	72 (58.1)	301 (50.0)	0.102	0 (0.0)
Body mass index, kg/m ²				0.064	85 (11.7)
< 18.5	75 (10.3)	7 (5.6)	68 (11.3)		
18.5-24.9	371 (51.1)	58 (46.8)	313 (52.0)		
25.0-29.9	181 (24.9)	40 (32.3)	141 (23.4)		
≥ 30.0	99 (13.6)	19 (15.3)	80 (13.3)		
Active malignant disease or AIDS	41 (5.6)	6 (4.8)	35 (5.8)	0.668	0 (0.0)
Chronic obstructive pulmonary disease	105 (14.5)	25 (20.2)	80 (13.3)	0.048	0 (0.0)
Diabetes	56 (7.7)	10 (8.1)	46 (7.6)	0.872	0 (0.0)
Heart disease	196 (27.0)	35 (28.2)	161 (26.7)	0.735	0 (0.0)
Co-morbid liver cirrhosis	29 (4.0)	6 (4.8)	23 (3.8)	0.598	0 (0.0)
Co-morbid chronic disease	202 (27.8)	42 (33.9)	160 (26.6)	0.099	0 (0.0)
ASA score				< 0.001	7 (1.0)
1	140 (19.3)	12 (9.7)	128 (21.3)		
2	241 (33.2)	29 (23.4)	212 (35.2)		
3	270 (37.2)	62 (50.0)	208 (34.6)		
4	69 (9.5)	21 (16.9)	48 (8.0)		
5	6 (0.8)	0 (0.0)	6 (1.0)		
Use of anticoagulants	60 (8.3)	17 (13.7)	43 (7.1)	0.016	2 (0.3)
Use of aspirin	185 (25.5)	42 (33.9)	143 (23.8)	0.019	2 (0.3)
Use of steroids	66 (9.1)	11 (8.9)	55 (9.1)	0.933	4 (0.6)
Use of NSAIDs	173 (23.8)	33 (26.6)	140 (23.3)	0.441	3 (0.4)
Alcohol abuse ^b	115 (15.8)	23 (18.5)	92 (15.3)	0.364	18 (2.5)
Daily smoking	389 (53.6)	63 (50.8)	326 (54.2)	0.496	35 (4.8)
Surgical delay > 6 h ^c	371 (51.1)	71 (57.3)	300 (49.8)	0.132	13 (1.8)
Gastric ulcer	412 (56.7)	73 (58.9)	346 (57.5)	0.600	47 (6.5)

ASA = American Society of Anesthesiologists; NSAID = non-steroidal anti-inflammatory drug.

a) Chi-square test.

b) Alcohol abuse is defined as > 36 g alcohol/day (men) or > 24 g alcohol/day (women).

c) Time from admission to surgery > 6 h.

Baseline and clinical characteristics among 726 patients with peptic ulcer perforation in Denmark, 1 September 2011-31 August 2013.

TABLE 2

Crude and adjusted association between re-operative surgery and body mass index among 726 patients with peptic ulcer perforation in Denmark, 1 September 2011-31 August 2013. Odds ratio with 95% confidence interval.

BMI, kg/m ²	Re-operative surgery, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
18.5-24.9	371 (51.1)	1.00 (ref.)	1.00 (ref.)
< 18.5	75 (10.3)	0.557 (0.226-1.376)	0.456 (0.181-1.148)
25.0-29.9	181 (24.9)	1.690 (1.003-2.845)	1.468 (0.857-2.517)
≥ 30.0	99 (13.6)	1.598 (0.838-3.049)	1.314 (0.663-2.601)

ASA = American Society of Anesthesiologists; BMI = body mass index; CI = confidence interval; OR = odds ratio.

a) Adjusted for the following covariates: age > 65 yrs (yes/no); co-morbidity (yes/no); ASA grade 3-5 (yes/no); and surgical delay > 6 h (yes/no).

multiple imputation; the preferred way of handling data that are not MCAR [13]. Limitations include confounding, counting residual confounding and confounding by indication, which is unavoidable in observational studies, and baseline imbalance. Accordingly, no conclusions on causal relationships can be given. Finally, the results of the present study should not be applied uncritically to PPU patients with a different case mix.

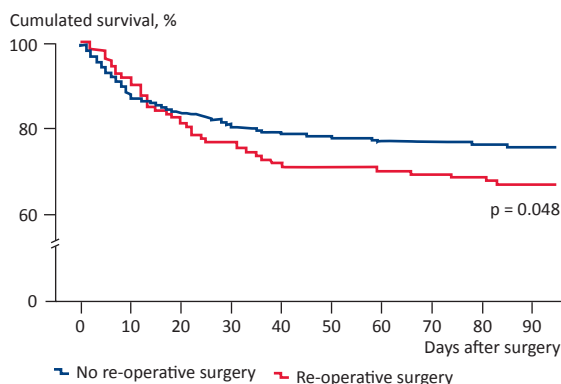
Obesity is considered a prognostic factor for poor outcome in a variety of surgical procedures [7, 9], and it is believed that obesity and its related medical co-morbidities increase the risk of an adverse outcome in general surgery [8]. Furthermore, it has been demonstrated that reoperative surgery is associated with increased mortality in gastrointestinal surgery [4]. In the present cohort of PPU patients, we found no association between overweight or obesity and reoperative surgery, but patients requiring reoperative surgery had a lower crude 90-day survival than patients not undergoing re-

operation. Recently published papers have failed to identify increased BMI as a prognostic factor for major death and post-operative complications, including reoperative surgery. In a prospective cohort study of patients undergoing general surgery, no independent association between obesity and major post-operative complications or death was shown [10], and in a large prospective multicentre cohort study in patients undergoing general surgery, a statistically significantly lower risk of mortality and reoperative surgery was observed in obese patients compared with normal-weight patients [8]. In contrast, two recent observational studies in elective general surgery found a higher incidence of anastomotic leakage with increasing BMI. A cohort study of patients undergoing elective resection of oesophageal found a linear association between increasing BMI and anastomotic leakage, and speculated that this could be due to a compromised vascularity of the conduit because of an increased tension on the conduit in the thoracic compartment or because of medical co-morbidities in general, such as diabetes or cardiovascular disease [7]. In a large cohort study of patients undergoing colonic cancer surgery, BMI > 30 kg/m² was shown to be an independent risk factor for anastomotic leakage [9]. Treatment of PPU is primarily done by suturing of the defect and placement of an omental patch, and it is in general considered a less extensive surgical procedure [4]. This may in part explain the discrepancy in relation to the increased risk of reoperation found in oesophageal and colonic surgery.

In several studies in general surgery, obese patients have been shown to have an increased risk of developing post-operative wound infections [8, 10]. This may be related to the presence of excessive fatty tissue with a low regional oxygen tension, which may predispose to impaired wound healing [7]. Wound infections can lead to deep infection, wound dehiscence and sepsis which, in turn, can lead to inadequate perfusion and healing, which increases the risk of surgical complications, including reoperative surgery [16]. However, the listed studies did not identify obesity as an independent risk factor for major post-operative complications including reoperation or death. Sepsis is believed to account for 40-50% of fatalities after PPU [2]. The apparent lack of association between increased BMI and reoperation in PPU is in accordance with the findings in a recent large multicentre cohort study of obese patients with septic shock. A lower crude hospital mortality of obese patients with septic shock than of patients with normal-range BMI was observed [17]. Correspondingly, a large prospective multicentre cohort study of patients undergoing general surgery found a significantly lower risk of sepsis/septic shock in the obese subjects [8]. Several other studies have rediscovered that despite their often

FIGURE 1

Crude 90-day cumulated survival according to re-operative surgery among 726 patients with peptic ulcer perforation in Denmark, 1 September 2011-31 August 2013.



severe medical co-morbidities, obese surgical patients and obese, critically ill patients have a lower mortality than normal-weight patients [18, 19]. An explanation for this “obesity paradox” may be that not only do obese patients have a sufficient nutritional reserve, but the obesity itself is believed to result in a chronic inflammatory state in the metabolically active tissue [20]. This results in a more efficient metabolic state where the body is “primed” to mount the appropriate inflammatory response to the stress of critical illness [8, 20]. Consequently, obese patients are believed to have a survival benefit over normal-weight patients in these extreme settings [8]. In the present study, obese PPU patients had the same risk as normal-weight patients for reoperative surgery. This is in line with a recently published paper where no statistically significant association between increased BMI and outcome was found in PPU patients [6]. Consequently, it does not seem that increased BMI plays a crucial role in survival and post-operative complications of PPU patients.

In the present nationwide cohort study of 726 PPU patients undergoing surgery between 2011 and 2013, no statistically significantly adjusted correlation between BMI and re-operation rates was found.

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