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ORIGINAL CONTRIBUTIONS

All-Cause Mortality Following Bariatric Surgery in Smokers and Non-smokers

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Abstract

Introduction Bariatric surgery is associated with lower all-cause mortality, but many studies exclude smokers. We sought to determine if the association of mortality and bariatric surgery differs between smokers and non-smokers.

Materials and Methods We conducted a retrospective cohort study in a large Israeli integrated payer/provider health care organization. A total of 7747 adult patients who underwent bariatric surgery between January 1, 2005, and December 31, 2014, were selected and compared with non-surgical patients (and were matched on age, sex, diabetes, and BMI using a sequential/simultaneous stratification matching). A total of 30,742 patients with a median follow-up of 4.3 years were included in this study with less than 1% lost to follow-up. The type of bariatric surgery (gastric banding, Roux-en-Y gastric bypass, or sleeve gastrectomy) and smoking status were determined from electronic health records. The rate of all-cause mortality in matched surgical and non-surgical patients was compared in smoking and non-smoking subgroups, adjusted for key potential confounders.

Results There was a statistically significantly higher mortality associated with not having bariatric surgery in both smoking (HR, 1.99; 95% CI, 1.54–2.56) and non-smoking (HR, 1.93; 95% CI, 1.12–3.34) subgroups. Although smokers had higher rates of mortality overall (2.6% in smokers compared with 1.7% in non-smokers), the mortality hazard ratio (comparing matched non-surgical patients to surgical patients) did not differ significantly between smokers and non-smokers (p for interaction = .67).

Conclusions Bariatric surgery was associated with significantly lower mortality in both smokers and non-smokers.

Keywords Bariatric surgery · Roux-en-Y gastric bypass · Gastric banding · Sleeve gastrectomy · Mortality · Subgroups

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Introduction

Bariatric surgery is an increasingly common treatment for severe obesity. Mortality benefits have been reported in a number of studies [1, 2] but most studies have excluded smokers from enrollment or analyses. There is a lack of information about the risks and benefits of bariatric surgery in smokers, and in the USA, smokers are commonly excluded from consideration for bariatric surgery if they do not refrain from smoking for at least 6 weeks before the operation [3, 4]. The objective of this study was to determine mortality following bariatric surgery in a population where smokers were not routinely excluded from consideration for bariatric surgery.

Materials and Methods

The detailed methods for the study design, source population, study population (including matching), exposures, and outcome measurements have been published previously [5]. This study utilized a matched retrospective cohort design. The source population included patients enrolled in Clalit Health Services (Clalit), a payer/provider health care organization that insures more than half of the Israeli population (close to 4.5 million members). Clalit and the other Israeli health organizations are characterized by a low annual turnover of around less than 2% [6], facilitating nearly complete patient follow-up of study outcomes. The Clalit data warehouse includes administrative data with socio-demographic and clinic information, diagnoses (based on ICD-9 codes), hospital- and community-based encounters, imaging, laboratory results, and pharmaceutical history (including both prescriptions and dispensing).

Patients included in the study were 24 years or older as of the surgery date (or index date for matched controls) and had continuous membership in Clalit during the 3 years before surgery or index date (baseline period). This age was chosen since it represents the age when most Israeli adults will have completed military service and have entered the national health insurance system. Exclusion criteria included pregnancy during the 4 years prior to index date, missing body mass index (BMI) measurements, a BMI value of equal or less than 30 kg/m^2 in all BMI measurements, or documentation of severe comorbidities (active cancer, Crohn's disease, end-stage renal disease, or ascites) during the baseline period.

All Clalit patients who underwent bariatric surgery between January 1, 2005, and December 31, 2014, were identified (and sub-classified as gastric banding [GB], Roux-en-Y gastric bypass [RYGB], and sleeve gastrectomy [SG]) based on first indication of the relevant International Classification of Diseases, Ninth Revision (ICD-9) code (43.82; 44.31; 44.95; 44.96; 44.97; 44.98; 539.01; 539.09; 539.81; 539.89; 649.2; 649.21; 649.22; 649.23; 649.24; or V45.86). For each bariatric surgery patient, three matched non-surgical patients were selected according to age group (stratified by 5-year intervals), sex, diagnosis of diabetes (based on an algorithm which incorporates relevant ICD-9 diagnostic codes (250 and 250.x), HbA1c concentration, glucose levels, and diabetes medications [7]) and BMI (stratified by 5-unit intervals, from >30 to >50 kg/m^2) using a sequential/simultaneous (time-dependent) stratification matching [1, 8]. Non-surgical patients were considered as potential matched candidates at different points in time. Individuals who were selected as non-surgical matched patients who subsequently underwent a bariatric surgical procedure were censored at the time of their surgery from the non-surgical group and were not added to the surgical group. Surgical patients for whom suitable matches were not found were excluded. Each patient who had any repeat procedure was classified according to his or her initial surgery type.

For the purpose of this study, two smoking subgroups were defined (never or former smoker and current smoker, as reported by the patient to his/her general practitioner during the baseline period). At Clalit, annual assessment and recording of smoking status became a quality measure in 2006, resulting in high rates of completeness in the electronic health records (EHR). Patients are asked both about current smoking status (current, former, never) and pack-years of smoking exposure. Individuals with missing smoking status during the baseline period ($n = 2798$) were excluded from the analysis.

All baseline measurements were taken from the Clalit's EHR repository, including socioeconomic characteristics: age (years), biological sex, socioeconomic status (low or medium/high), population sector (Jewish or non-Jewish), and immigrant status (immigrated to Israel or born in Israel). Population sector (Jewish or non-Jewish) and socioeconomic status (SES; low or medium/high) can be determined only at the clinic level in accordance with the designation of each member's primary care clinic, based on census designations from the Israeli Central Bureau of Statistics. Clinical covariates included body mass index (kg/m^2), diagnosis of hyperlipidemia, diagnosis of CVD, diagnosis of hypertension, high-density lipoprotein cholesterol, and triglycerides. Medical diagnoses as of the index date were defined based on ICD-9 codes extracted from hospital discharge records or ambulatory medical records. Ambulatory records with no ICD-9 code were identified based on basic natural language processing of available text. Medication use was assessed through Clalit records of prescriptions filled as coded in the Anatomical Therapeutic Chemical classification system.

All-cause mortality (yes or no) during the follow-up period was the primary outcome. Information regarding mortality events was obtained from Ministry of Interior data, which includes current and complete information for the entire Israeli population. Israelis who emigrate from Israel are still tracked in this database resulting in lost to follow-up for

purposes of tracking mortality of less than 1%. Additional clinical outcomes included major adverse cardiac event (MACE, defined as myocardial infarction, unstable angina, or coronary artery bypass graft), hospitalization at least 30 days after the index date, and non-bariatric reoperation (including hernia, bowel obstruction, and bleeding ulcer taken from hospital discharge summaries). This study was approved by the Clalit Health Services institutional review board. As the study used deidentified existing medical records, patient consent was not required.

Statistical Analysis

The main characteristics of the total study population, stratified by smoking status and surgery type, were described using proportions for categorical variables and means with standard deviations or medians with interquartile ranges for continuous variables. Differences between surgical patients and their matched non-surgical patients were evaluated using the unpaired *t* test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables.

For regression models, patient characteristic data were imputed using the R package MICE version 2.22 applying chained equations. Cox proportional hazards regression was employed to assess the hazard ratio (HR) for mortality (comparing those who did not have bariatric surgery with matched surgical patients). In addition to the variables included in the matching (age, sex, diagnosis of diabetes, and BMI group), the following potential confounders were included in the adjusted Cox models: age (years), sex (male, female), SES (low, medium/high), population sector (Jewish, non-Jewish), immigrant status (immigrated to Israel, born in Israel), diagnosis of hyperlipidemia (yes, no), diagnosis of CVD (yes, no), BMI (kg/m^2), diagnosis of hypertension (yes, no), high-density lipoprotein cholesterol (mg/dL), and triglycerides (mg/dL). Effect modification of the relationship of surgery and mortality by smoking was established from the significance of the interaction term (smoking status × surgery) in Cox regression models. Stratified Cox proportional hazards regression using multiple-matched pairs (3:1) was employed as a sensitivity analysis. HR estimates were also calculated separately for each smoking subgroup using Cox regression models.

Results

The final sample size consisted of 7747 surgical patients and 22,995 matched non-surgical patients. A total of 1362 patients had Roux-en-Y gastric bypass surgery, 3360 patients had sleeve gastrectomy surgery, and 3025 patients had gastric band surgery. Table 1 shows the baseline and post-surgical population characteristics for participants who had bariatric surgery and their matched controls, for the total population, and broken down by smoking subgroups. Supplementary Table 1 shows the same information and is further broken down by the type of bariatric surgery. The median follow-up time was 4.3 years. At the time of surgery, 22.8% of the surgical patients were current smokers (20.1% of Roux-en-Y patients, 20.6% sleeve gastrectomy patients, and 26.4% of gastric banding patients); 19.8% of matched controls were current smokers. Because we did not originally match patients on smoking, there were some significant differences in the distribution of gender and prevalent diabetes when comparing surgical patients and matched controls across smoking subgroups. Across all smoking subgroups and all (surgery type × smoking) subgroups, surgical patients had lower mortality rates than non-surgical controls. Hospitalization rates at least 1 month after surgery (or index date for non-surgical patients) were higher in surgical cases in both smoking and non-smoking subgroups. Non-bariatric reoperations for hernia, bowel obstruction, and bleeding ulcer were 3–4 times higher in surgical patients compared with non-surgical controls across all smoking subgroups.

Table 2 presents the HR for mortality comparing those who did not have bariatric surgery to matched surgical patients, by smoking subgroup for the total study population, and divided by surgical subtype. In both (never or former) smokers (HR, 1.93; 95% CI, 1.12–3.34) and current smokers (HR, 1.99; 95% confidence interval [CI], 1.54–2.56), there was a statistically significant association of bariatric surgery with lower mortality; the *p* value for effect modification by smoking was not statistically significant ($p = .67$), indicating the HRs were not statistically significantly different between the smoking subgroups. HRs also indicated an association of bariatric surgery with lower mortality in all smoking subgroups for all subtypes of bariatric surgery (GB, RYGB, and SG), although these results should be interpreted with caution as some of the 95% confidence intervals are very wide and overlap zero. In sensitivity analyses, HR estimates and 95% CIs were similar for both stratified and unstratified Cox models. Specifically, the HR comparing those who did not have surgery with those who did among participants who were current smokers was 1.99 (95% CI, 1.54–2.56) in the unstratified Cox model and 1.93 (95% CI, 1.38–2.48) in the stratified Cox model.

Discussion

We compared the rates of total mortality for patients who underwent bariatric surgery with matched individuals who did not have surgery across smoking subgroups. Among both smokers and non-smokers, bariatric surgery was significantly associated with lower mortality. The magnitude for the association between surgery and mortality was similar (HR, 1.99

Table 1 Baseline and post-surgical characteristics of the bariatric surgery patients and matched non-surgical patients in the total population and by smoking status

	Total surgical patients, $n = 7747$	Total non-surgical patients, $n = 22{,}995$	$p < .05$ surgery vs non-surgery	Current smoking surgical patients, $n = 1765$	Current smoking non- surgical patients, $n = 4562$	$p < .05$ surgery vs non-surgery	Current non-smoking surgical patients, $n = 5982$	Current non-smoking non-surgical patients, $n = 18{,}433$	$p < .05$ surgery vs non-surgery
Follow-up in years, mean (SD)	4.5 (2.2)	4.2 (2.2)	yes	4.8 (2.5)	4.2 (2.3)	yes	4.3 (2.1)	4.1 (2.2)	yes
Range in years	.1–11	.1–11		.1–11	.1–11		.1–11	.1–11	
Baseline									
Age in years, mean (SD)	45.8 (11.3)	46.0 (11.4)		43.1 (10.6)	43.5 (11.1)		46.6 (11.4)	46.6 (11.3)	
Male sex, %	35.0%	34.7%		42.1%	53.4%	yes	32.8%	30.1%	yes
Prevalent diabetes, %	29.6%	29.7%		23.9%	29.2%	yes	31.3%	29.8	yes
BMI (kg/m^2) $30 \leq \times < 45$, %	81.9%	82.3%		85.2%	83.8%		80.9%	81.9%	
BMI (kg/m^2) ≥ 45, %	18.1%	17.7%		14.8%	16.2%		19.1%	18.1%	
Current smoker, %	22.8%	19.8%	yes						
Ever smoker, %	41.5%	32.3%	yes						
Post-surgical									
Number of deaths	92	500		26	138		66	362	
Mortality, %	1.2%	2.2%	yes	1.5%	3.0%	yes	1.1%	2.0%	yes
MACE	3.4%	3.2%		3.8%	4.8%		3.3%	2.9%	yes
Hospitalization (more than 1 month after surgery)	41.3%	35.7%	yes	44.7%	40.6%	yes	40.2%	34.4%	yes
Non-bariatric reoperation (hernia, bowel obstruction, bleeding ulcer)	9.2%	2.8%	yes	8.6%	2.9%	yes	9.4%	2.8%	yes

BMI, body mass index; *MACE*, major adverse cardiac event

Table 2 Hazard ratios for mortality, comparing those patients who did not have bariatric surgery with matched surgical patients, in different subgroups

Subgroup	Number of deaths during follow-up period	Mortality HR, all procedures (CI)	*p* value for effect modification across subgroups	Mortality HR, GB (CI)	Mortality HR, RYGB (CI)	Mortality HR, SG (CI)
All	592	1.97 (1.51, 2.58)	NA	2.03 (1.38, 2.98)	2.59 (1.56, 4.29)	1.48 (1.07, 2.04)
Never or former smoker	428	1.93 (1.12, 3.34)	0.67	1.97 (1.28, 3.04)	2.18 (1.25, 3.80)	1.41 (0.97, 2.04)
Current smoker	164	1.99 (1.54, 2.56)	0.67	2.29 (1.00, 5.22)	4.72 (1.42, 15.64)	1.73 (0.87, 3.42)

All analyses were based on multiple imputed data run in unstratified Cox models. All models adjusted for the following baseline variables: age (years), sex (male or female), body mass index (kg/m^2), smoking status (current smoker or non-smoker/former smoker), socioeconomic status (low or medium/high), population sector (Jewish or non-Jewish), immigrant status (immigrated to Israel or born in Israel), diagnosis of hyperlipidemia (yes or no), diagnosis of CVD (yes or no), diagnosis of hypertension (yes or no), high-density lipoprotein cholesterol (log-transformed of the continuous level), and triglycerides (log-transformed of the continuous level)

p value for effect modification was calculated based on unstratified Cox model which included all covariates described above and the interaction term: smoking status (current or never/former) × surgery status

HR, hazard ratio; *CI*, confidence interval; *GB*, gastric banding; *RYGB*, Roux-en-Y gastric bypass; *SG*, sleeve gastrectomy; *NA*, not applicable

and HR, 1.93, not statistically significantly different) among smokers and non-smokers.

In Israel, smokers are urged to quit smoking during pre-bariatric surgical consultations, but those who are unable to quit are not precluded from having surgery. In the USA, the recommendation (according to the Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient – 2013 update) is that patients who smoke cigarettes should stop, preferably at least 6 weeks before bariatric surgery [3]. In practice, many surgeons screen for blood or urine nicotine and either refuse to schedule surgery in patients who smoke or cancel surgeries if lab results indicate any use of nicotine before surgery. An often-cited reason for the US practice with regard to nicotine is a 1999 study, which showed a twofold death rate after bariatric surgery over long-term follow-up in smokers compared with non-smokers. However, this study included surgeries that took place between 1986 and 1999 (when surgical techniques were very different) and, more importantly, did not compare mortality rates with matched non-surgical controls [9]. Although smokers may have higher rates of death following bariatric surgery than non-smokers (as do smokers compared with non-smokers overall), our data suggest that smokers experience a similar association with lower mortality following surgery.

It is important to note, however, that the primary rationale given for the US recommendations is due to demonstrated higher rates of poor wound healing and anastomotic ulcers in smokers compared with non-smokers [3], as well as higher rates of surgical adverse outcomes, such as difficulty weaning from a ventilator [10]. A 2014 study from the National Surgical Quality Improvement Program database showed any smoking within the year prior to surgery to be significantly associated with higher rates of organ space infection, prolonged intubation, reintubation, pneumonia, sepsis, shock, and longer length of stay, but not to be significantly associated with 30-day mortality [11]. Interestingly, a 2018 study from the Michigan Bariatric Surgery Collaborative reported a significant association between recent smoking (quitting between 3 and 12 months before surgery compared with never smoking) and severe operative complications in patients undergoing Roux-en-Y surgery, but not in patients undergoing sleeve gastrectomy surgery [12]. As these studies were conducted in the USA, they likely included few patients currently smoking at the time of surgery. Our study did not capture short-term outcomes like surgical complications, but instead focused on long-term outcomes after surgery. Therefore, the association of current smoking with short-term complications after bariatric surgery as well as the association of bariatric surgeries with mortality in smokers and non-smokers should be further examined in datasets that include patients operated on within the last decade. If additional results support a similar association of mortality with bariatric surgery in smokers and non-smokers with only modest observed associations between smoking and surgical complications, policies requiring complete abstinence from nicotine for 6 weeks prior to surgery should potentially be revisited, with consideration for allowing surgeries in selected smokers who attempt, but are unable to quit.

There were limitations to our analysis. Although we tried to exclude for contraindications for surgery (such as active cancer, Crohn's disease, end-stage renal disease, and ascites), it is possible that some matched controls had contraindications for bariatric surgery; inclusion of these individuals in our study as matched non-surgical patients could bias our estimates of survival away from the null. There is a slight possibility that bariatric surgical procedures were missed in the matched controls, and thus, controls could have been inappropriately included. Because we did not match on

smoking status when we assembled this cohort, there may be residual confounding by age, sex, or prevalent diabetes within our smoking subgroups, although we did control for all these variables in our regression analysis. The use of ICD-9 codes, particularly in the assessment of major adverse cardiac event and reoperations for hernia, bowel obstruction, or bleeding ulcer post-surgery (or post-index date), may also have misclassified some participants on these outcomes.

There was also a potential for the misclassification of smoking if patients (a) misreported smoking status to their doctor or (b) changed smoking status between the date it was recorded in the EHR and surgery or index date. Because smoking is not an absolute contraindication to bariatric surgery in Israel, we believe that this type of misclassification was largely non-differential. The rate of 22.8% of patients who considered themselves smokers at the time of bariatric surgery matches closely with estimates of smoking prevalence from the Israeli Ministry of Health (https://www.health.gov.il/English/Topics/KHealth/smoking/Pages/SmokingRatesInIsrael.aspx). In addition, these results may not be generalizable to other geographic populations. However, the 2014 World Health Organization (WHO) Global Status Report on Non-Communicable Diseases [13] demonstrated many similarities between health and health care in the USA and Israel: Israel is listed by the WHO as a high-income country. The percentage of individuals who are overweight is similar in both countries, as are the rates of obesity-related morbidities (age-standardized diabetes prevalence in Israel, 6.2% vs. in the USA, 7.7%). The criteria for surgery (BMI > 40 kg/m^2, or > 35 kg/m^2 with comorbidities) are identical in the two countries. Finally, the results broken down by surgical subtype should be interpreted with caution given the smaller sample sizes and larger confidence intervals in for calculations of mortality HR in these groups. Strengths of the study included very large numbers of both surgical and non-surgical patients and nearly complete availability of follow-up data within the health care system, including nearly complete capture of mortality.

Bariatric surgery is associated with significantly lower mortality in both smokers and non-smokers. If this conclusion is replicated in other studies, this information should potentially be considered when making policies with regard to bariatric surgery in current smokers.

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Compliance with Ethical Standards

This study was approved by the institutional review board of Clalit Health Service. For this type of study, formal consent is not required.

Conflict of Interest The authors declare that they have no conflicts of interest.

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