A Simple Prediction Rule for All-Cause Mortality in a Cohort Eligible for Bariatric Surgery

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Importance  Current eligibility criteria for bariatric surgery use arbitrarily chosen body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) thresholds, an approach that has been criticized as arbitrary and lacking evidence.

Objectives  To verify the importance of BMI as a mortality predictor, to identify other important mortality predictors, and to construct a mortality prediction rule in a population eligible for bariatric surgery.

Design  We studied individuals from a population-representative register who met contemporary eligibility criteria for bariatric surgery (BMI, ≥35.0 alone or 30.0-34.9 with an obesity-related comorbidity) from January 1, 1988, through December 31, 1998. We used binary logistic regression to construct a parsimonious model and a clinical prediction rule for 10-year all-cause mortality.

Setting  The United Kingdom General Practice Research Database, a population-representative primary care registry.

Participants  Fifteen thousand three hundred ninety-four patients aged 18 to 65 years.

Exposure  Bariatric surgery.

Main Outcome and Measure  Ten-year all-cause mortality.

Results  Mean (SD) age was 46.9 (11.9) years, BMI was 36.2 (5.5), and 63.2% of the patients were women. All-cause mortality was 2.1%, and mean follow-up duration was 9.9 years. The final model, which included age (odds ratio, 1.09 per year [95% CI, 1.07-1.10]), type 2 diabetes mellitus (2.25 [1.76-2.87]), current smoking (1.62 [1.28-2.06]), and male sex (1.50 [1.20-1.87]), had a C statistic of 0.768. Although BMI significantly predicted mortality (odds ratio, 1.03 per unit [95% CI, 1.01-1.05]), it did not improve model discrimination or calibration. We divided clinical prediction rule scoring into 4 tiers. All-cause mortality was 0.2% in tier 1, 0.9% in tier 2, 2.0% in tier 3, and 5.2% in tier 4.

Conclusions and Relevance  All-cause 10-year mortality in obese individuals eligible for bariatric surgery can be estimated using a simple 4-variable prediction rule based on age, sex, smoking, and diabetes mellitus. Body mass index was not an important mortality predictor. Further work is needed to define low, moderate, and high absolute risk thresholds and to provide external validation.

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Global uptake of bariatric surgery, considered the most effective treatment currently available for severe or medically complicated obesity, has increased 8-fold during the past decade to 350,000 procedures annually. Surgery is associated with 24% (95% CI, 0.01-0.41) reductions in 10-year all-cause mortality, substantial increases in type 2 diabetes mellitus remission rates, and improvements in other obesity-related comorbidities and quality of life.1-4

Eligibility criteria for bariatric surgery, originally proposed during a 1991 US National Institutes of Health (NIH) consensus conference,5 endorse surgery for patients with treatment-refractory obesity measured by a body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 35.0 to 39.9 with a major obesity-related comorbidity or by a BMI of 40.0 or greater. New evidence supporting the use of surgery in patients with a BMI less than 35.0 has prompted expansion of these criteria.6,7 Recently, the US Food and Drug Administration approved gastric banding (but not other procedure types) for patients with a BMI greater than 30.0 and a major obesity-related comorbidity.8 Similarly, the International Diabetes Federation9 expanded eligibility for all bariatric procedures to patients with type 2 diabetes mellitus and class 1 obesity (BMI, 30.0-34.9).

Therefore, although individuals with medically complicated class 1 obesity constitute the broadest group currently considered eligible for bariatric surgery, potential eligibility (which determines access and reimbursement) varies widely according to BMI, comorbidity presence, and procedure type. This variation means that a prioritization or triage system is implicitly being used to determine who does and does not receive surgery among those individuals generally considered eligible.10-12 Current criteria are structured such that a 5-unit increment in BMI (ie, 35.0-40.0) obviates any further requirement for obesity-related comorbidity. In addition, under the original NIH criteria, different obesity-related comorbidities are considered to be of equal importance for eligibility determination. Conversely, recent reductions in the BMI thresholds for type 2 diabetes mellitus imply that this comorbidity should be considered more important than others. Other than data demonstrating that type 2 diabetes mellitus is highly responsive to surgery,13 to our knowledge, no other published data validate these concepts. In fact, the choice of BMI thresholds has been criticized as arbitrary and lacking evidence.14,15

The objective of this study was to identify mortality predictors within a sample of patients eligible for bariatric surgery that was derived from a large population-representative primary care registry. Examining the importance of BMI as a mortality predictor was an explicit aim. Specifically, we sought to construct a parsimonious clinical prediction rule for all-cause mortality composed of commonly available, clinically relevant predictor variables. We believed that such a rule would help to identify and summarize key prognostic indicators and calculate individual mortality risk.

Methods

Data Sources
The University of Alberta research ethics board approved the study protocol. Informed consent to conduct this secondary analysis of existing registry data was not required. We analyzed data from the UK General Practice Research Database (GPRD) (recently amalgamated into the Clinical Practice Research Datalink), the world’s largest, most comprehensive computerized database of anonymized, linked longitudinal medical records.15,16 The GPRD contains population-representative data from more than 600 UK primary care practices (6% of the UK population).15,16 The United Kingdom has a comprehensive national health care system, 98% of UK residents are registered in a general practice, and all care is centralized within the general practice record.17-19

The GPRD contains the complete primary care record, including patient demographics (eg, age and sex) and health behaviors (eg, alcohol intake and smoking), physiological and laboratory data (blood pressure, BMI, blood glucose levels, and cholesterol level profile), clinician-assigned diagnoses and disease registries for hypertension and type 2 diabetes mellitus, and outpatient prescription medications. Medical diagnoses are coded using the Oxford Medical Information System and Read codes.15,16,20

Validation of GPRD data is performed on an ongoing basis in accordance with standardized guidelines that certify certain practices as up-to-standard or of research quality. More than 350 validation studies have been performed, and more than 700 peer-reviewed studies have been published.20 A systematic review of more than 200 studies found GPRD medical diagnostic coding to be highly accurate (a median of 89% of medical diagnoses confirmed as accurate).20 Drug exposure data have been similarly validated and found to be of equally high quality.16,21 Active smoking data are 80% accurate compared with population-based survey data.22 Although BMI is measured annually in only one-half to two-thirds of GPRD patients, 99.2% of obese patients have at least 1 BMI measurement recorded during a 10-year span.23 Only 0.6% of BMI values in the GPRD have been found to be inconsistent or implausible.23

Study Population
We studied adults (aged 18-65 years) registered with GPRD up-to-standard practices from January 1, 1988, through December 31, 1998, and considered eligible for bariatric surgery. An age cutoff of 65 years was chosen because very few bariatric procedures are performed in patients older than 65 years.24 For the primary analysis, in accordance with contemporary recommendations, we considered patients with a BMI of 35.0 or greater or a BMI of 30.0 to 34.9 with an obesity-related comorbidity to be eligible for surgery.8,9,25 Hypertension, dyslipidemia, heart failure, type 2 diabetes mellitus, sleep apnea, osteoarthritis, coronary artery disease, and cerebrovascular disease (CVD) were obesity-related comorbidities used to define eligibility.25

The index date, defined as the date of initial cohort entry, corresponded to the first time a surgery-eligible BMI was recorded. We excluded patients with any of the following contraindications to surgery, which were defined using medical (Read) codes and/or by medication use (within the year before the index date): pregnancy, suicidality, psychosis, severe (medication-refractory) depression, bulimia, active cancer, and
prior bariatric surgery. We also performed a subgroup analysis in patients meeting the original NIH eligibility criteria for surgery. To evaluate the potential impact of unrecognized serious baseline illness, we also performed a sensitivity analysis after excluding early deaths (mortality within 6 months of the index date).

Primary Outcome
The primary outcome, 10-year all-cause mortality, was ascertained by linking with the mortality records of the UK Office of National Statistics. These mortality records undergo frequent and extensive assessment to verify accuracy and validity; registration of all deaths in the United Kingdom is required by law. Each patient was followed up until death or for 10 years. A 10-year time horizon was chosen because it is considered clinically relevant and is widely used for nonbariatric risk prediction.

Chronic Health Behaviors and Obesity-Related Comorbidities
We focused on clinically important, relatively common chronic comorbidities that had well-documented associations with obesity or all-cause mortality and are readily identified in most clinical settings. In addition to age, sex, and BMI, we modeled the impact of health behaviors (smoking and alcohol intake) and chronic medical conditions (hypertension, type 2 diabetes mellitus, dyslipidemia, stable depression, sleep apnea, heart failure, coronary artery disease, CVD, and gastroesophageal reflux disease). Comorbidities, smoking, and alcohol use were identified using disease registries or medical (Read) codes and/or by use of medication. Comorbidities were considered to be present at baseline if identified at any point before or within 3 months of the index date.

Statistical Analysis
We first examined descriptive variables and calculated means, medians, and proportions. Mortality was compared across BMI classes within age strata using Fisher exact tests. We originally intended to perform Cox proportional hazards regression to model time to death. Because the proportional hazards assumption was violated, we used binary logistic regression instead to predict 10-year all-cause mortality.

Similar modeling methods were used for the primary analysis (performed first), subgroup analysis, and sensitivity analyses. Age and BMI were modeled as continuous variables, and the remaining predictors were modeled as dichotomous variables. All variables were included in the initial model. Next, nonsignificant (P > .05) and then significant (P < .05) predictors were removed manually in stepwise fashion. We examined the effect of variable exclusion on the Akaike information criterion (to assess relative goodness of fit) and model C statistic (to assess discrimination). Variables with a minimal impact on both analyses were excluded to create a parsimonious final model.

Final model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. To further confirm that the exclusion of each predictor had a minimal effect on model predictive ability, we calculated a net reclassification improvement (NRI) index (performed separately for each variable). First, 4 mortality strata were chosen, with an upper limit of 5% (<1.75%, 1.75%-3.49%, 3.50%-4.99%, >5.00%), which indicates high-risk status according to expert consensus. Second, patients were categorized into these strata according to their predicted risk in models constructed with and without the predictor variable (performed separately in patients with and without events). Third, the between-model net change in the proportion of patients appropriately reclassified (by adding the predictor in question) was tabulated. The significance level for the NRI analysis was set at .1 (with P > .1 indicating that exclusion of the predictor variable from the model was appropriate).

A bootstrap analysis using 1000 replicative cycles with replacement was performed to internally validate our findings and verify the magnitude, 95% confidence intervals, and statistical significance of the final β coefficient estimates. Clinical prediction rule scoring weights were created for each variable in the final model by dividing each β coefficient by the smallest model coefficient and rounding up to the nearest integer. We used commercially available statistical software (SAS, version 9.3 [SAS Institute Inc] and R, version 2.15.0 [http://cran.r-project.org/bin/windows/base/old/2.15.0]) for the analyses.

Further sensitivity analyses were added after peer review. First, we examined the effect of adding quadratic terms for age and BMI (to assess for a nonlinear relationship with mortality) on the C statistic. Second, we constructed an accelerated failure time model for survival analysis, which does not assume proportional hazards, to assess whether the results were consistent with logistic regression.

Results
Baseline Characteristics
The initial sample size was 17,340 patients; of these, 1946 (11.2%) were excluded (Supplement eFigure). Included and excluded patients had similar mean (SD) age (46.9 [11.9] vs 47.3 [12.0] years), BMI (36.2 [5.5] vs 35.7 [5.7]), and sex distribution (63.2% vs 64.1% female). Baseline characteristics of the final cohort (n = 15,394) are summarized in Table 1. Mean (SD) duration of follow-up was 9.9 (0.6) years.

Rates and Correlates of Mortality
All-cause 10-year mortality was 2.1% (n = 330). Mortality within age strata did not differ significantly between BMI classes (P > .05) (Figure). Age, type 2 diabetes mellitus, male sex, smoking, BMI, coronary artery disease, and CVD were significant predictors of all-cause mortality, with age and diabetes having the largest impact (Table 2). Exclusion of other variables not significantly associated with all-cause mortality had minimal effect on the Akaike information criterion statistics (2908.6 before vs 2901.5 after exclusion) and C statistic (0.771 vs 0.768). Body mass index and CVD contributed minimally to the Akaike information criterion (2901.5 before vs 2910.2 after exclusion) and C statistic (0.768 vs 0.762) and were then excluded for the sake of parsimony. The NRI indexes confirmed that their exclusion was appropriate (NRI index for BMI, 2.0% [P = .15]; for coronary artery disease, 0.6% [P = .35]; and for CVD, 1.8% [P = .13]).
Age (odds ratio, 1.09 per year [95% CI, 1.07-1.10]), type 2 diabetes mellitus (2.25 [1.76-2.87]), current smoking (1.62 [1.28-2.06]), and male sex (1.50 [1.20-1.87]) constituted the final model (Table 2), with \(P = .99\) for overall goodness of fit. The bootstrap method analysis produced variance estimates and \(P\) values of identical magnitude to those found in the primary analysis.

Clinical Prediction Rule
The 4-variable clinical prediction rule scores ranged from 0 to 107. To simplify use of the prediction rule, scores were categorized into 4 tiers (Table 3). Mortality ranged from 0.2% for tier 1 to 5.2% for tier 4 (Table 3).

Sensitivity and Subgroup Analyses
First, results were unchanged after excluding early deaths (data not shown). Second, patients meeting NIH eligibility criteria (n = 5071) included 118 deaths (2.3%). Age (odds ratio, 1.08 [95% CI, 1.05-1.10]), type 2 diabetes mellitus (2.98 [2.02-4.34]), and CVD (2.82 [1.36-5.88]) were significant predictors of mortality (C statistic, 0.763). Body mass index was not a significant predictor of mortality, and exclusion of BMI again had no effect on model variables. The C statistic changed little after excluding CVD (0.762); however, the NRI index (7.3% \([P = .03]\)) indicated that this variable should be retained in the model. Third, adding quadratic terms for BMI and age did not improve model C statistics (data not shown). Fourth, the accelerated failure time model results were identical to those of the primary analysis (Supplement [eTable]).

Discussion
In a study of 15,394 patients who were eligible for bariatric surgery, all-cause 10-year mortality was 2.1%. The main drivers of mortality were age and type 2 diabetes mellitus. Although their association with the outcome was statistically significant, established CVD and BMI did not contribute materially to the mortality prediction in the primary analysis. Our results challenge conventional wisdom emphasizing the importance of BMI as a prognostic indicator for mortality in indi-
Prediction Rule for Mortality in Bariatric Surgery

Original Investigation  Research

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also differs from other risk engines in that it predicts all-
cause mortality rather than cardiovascular mortality or car-
diovascular events. As such, further work is needed to define

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Points Assigned</th>
<th>10-y All-Cause Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 1-y increase beyond 18 y</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>10</td>
<td>...</td>
</tr>
<tr>
<td>Current smoker</td>
<td>6</td>
<td>...</td>
</tr>
<tr>
<td>Male sex</td>
<td>5</td>
<td>...</td>
</tr>
<tr>
<td>Tier&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;sup&gt;a&lt;/sup&gt; Assigned by mortality risk. Points represent total possible points.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;20</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>20-39</td>
<td>0.9</td>
</tr>
<tr>
<td>3</td>
<td>40-59</td>
<td>2.0</td>
</tr>
<tr>
<td>4</td>
<td>≥60</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; CVD, cerebrovascular disease; OR, odds ratio.

<sup>a</sup> Calculated by χ<sup>2</sup> test.
<sup>b</sup> Includes all significant predictors.

Table 3. Clinical Prediction Rule

Table 2. Binary Logistic Regression Predicting All-Cause Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (SE), β Coefficient</th>
<th>Standardized Estimate, β Coefficient</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Point Estimate, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary model&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.08 (0.01)</td>
<td>0.54</td>
<td>&lt;.001</td>
<td>1.09 (1.07-1.10)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>0.81 (0.12)</td>
<td>0.15</td>
<td>&lt;.001</td>
<td>2.24 (1.76-2.86)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.49 (0.12)</td>
<td>0.12</td>
<td>&lt;.001</td>
<td>1.64 (1.29-2.08)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.41 (0.12)</td>
<td>0.11</td>
<td>&lt;.001</td>
<td>1.51 (1.21-1.90)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.03 (0.01)</td>
<td>0.08</td>
<td>.004</td>
<td>1.03 (1.01-1.05)</td>
</tr>
<tr>
<td>CVD</td>
<td>0.47 (0.24)</td>
<td>0.04</td>
<td>.045</td>
<td>1.60 (1.01-2.55)</td>
</tr>
<tr>
<td>CAD</td>
<td>0.28 (0.14)</td>
<td>0.05</td>
<td>.04</td>
<td>1.33 (1.01-1.75)</td>
</tr>
<tr>
<td>Final model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.08 (0.01)</td>
<td>0.54</td>
<td>&lt;.001</td>
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<td>0.11</td>
<td>&lt;.001</td>
<td>1.62 (1.28-2.06)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.40 (0.11)</td>
<td>0.11</td>
<td>&lt;.001</td>
<td>1.50 (1.20-1.87)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; CVD, cerebrovascular disease; OR, odds ratio.

<sup>a</sup> Calculated by χ<sup>2</sup> test.
<sup>b</sup> Includes all significant predictors.

To our knowledge, only 1 other study has examined the utility of an alternative staging system to BMI for mortality prediction in individuals eligible for bariatric surgery. In that population-representative US sample (n = 546), the Edmonton Obesity Staging System, a 5-point ordinal score, predicted mortality independently of BMI. However, a clinical prediction rule was not developed. Furthermore, the Edmonton Obesity Staging System is of limited practical utility because it is complex, depends on data elements that are not measured routinely (eg, functional status), and arbitrarily considers different obesity-related comorbidities to be of equivalent prognostic value.

The prediction rule constructed in the present study enables individual risk calculation and facilitates prognostic comparisons between different individuals. Unlike other commonly used contemporary risk engines, this prediction rule is specific to a population eligible for bariatric surgery and was constructed from a cohort containing a substantial proportion (17.3%) of severely obese individuals (BMI, ≥40.0). The rule also differs from other risk engines in that it predicts all-cause mortality rather than cardiovascular mortality or cardiovascular events. As such, further work is needed to define low, moderate, and high absolute risk thresholds. Other researchers have defined a 10-year cardiovascular mortality risk of 5% as high and indicative of the need for treatment of cardiovascular risk factors. Although a similar threshold could be considered in individuals eligible for bariatric surgery, a 10-year mortality rate of 5% is extremely high in relative terms considering the young age distribution of our cohort. Indeed, given a 10-year 1998 US general-population all-cause mortality base rate of 0.4% (among 20-year-old nonsmoking women), mortality increased 5-fold in tier 3 patients and more than 12-fold in tier 4 patients.

Individual mortality risk quantification might also be useful on a system management level to help inform decisions about allocating surgery where large demand-supply gaps exist. Worldwide, access to publicly funded bariatric surgery is limited and patients face protracted, multiyear wait times. No evidence-based allocation system currently exists, and a risk-treatment paradox has emerged (ie, compared with individuals eligible for surgery, surgical recipients are more likely to be at lower risk because they have a greater likelihood of being young, female, and free of comorbidity). Whether to incorporate individual risk quantification into allocation decisions and how best to do this and account for other impor-
tant factors (e.g., operative risk, expected surgery-related benefit, and nonmortality end points) remain unresolved and undefined.

Despite its novelty and strengths, this study has several limitations. First, we focused on all-cause mortality and did not examine other clinically important end points. Second, comorbidity prevalence was lower than expected prevalence estimates based on contemporaneous data.39 This unexpected finding could be related to systematic comorbidity underdiagnosis in this obese population and may have potentially biased odds ratio estimates toward the null. Third, we studied a sample from the United Kingdom eligible for bariatric surgery, which should be borne in mind when generalizing the results beyond the United Kingdom. Fourth, we used BMI levels to define cohort entry. Although more than 99% of obese surgery, which should be borne in mind when generalizing the sample from the United Kingdom eligible for bariatric surgery, would fit, and nonmortality end points) remain unresolved and undefined.

In conclusion, our findings demonstrate that factors other than BMI are important in predicting the risk of death in patients eligible for bariatric surgery and that, of the obesity-related comorbidities, type 2 diabetes mellitus is the most important mortality predictor. Given that diabetes mellitus is highly amenable to surgical treatment, a strong case could be made for prioritizing it over BMI or other comorbidities. Regardless, our findings call into question current practices, such as the inordinate emphasis placed on BMI increments of 5.0 embedded in contemporary eligibility criteria. Once our findings are externally validated, we believe that a clinical prediction rule similar to ours should be adopted to optimize delivery of bariatric care.

**REFERENCES**


