ANESTHESIOLOGY

Biodemography of Human Aging (Gompertz–Makeham Law) Applied to Surgical Mortality Modeling: A Retrospective National Cohort Study

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ABSTRACT

Background: The Gompertz–Makeham law describes a characteristic pattern of mortality in human populations where the death rate is near constant between ages 18 and 30 yr (Makeham law) and rises exponentially thereafter (Gompertz law). This pattern has not been described in surgical populations, but if true, it would have important implications for understanding surgical risk and design and interpretation of surgical risk models. The aim of this study was to determine whether the Gompertz–Makeham law applies to perioperative mortality risk and the conditions under which it may apply.

Methods: This study examined the relationship between age and 1-month postoperative all-cause mortality risk in a 10-yr New Zealand administrative dataset comprising 5,615,100 surgical procedures from 2007 to 2016. The dataset includes patient and surgical factors including procedures, American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status score, diagnoses, and other relevant details. Semilogarithmic graphs of mortality risk and age were plotted. Linear regression models were fitted, with regression line slope and Pearson correlation coefficient calculated.

Results: The primary outcome occurred in 114,782 (2.0%) of 5,615,100 included participants. The Gompertz–Makeham law seems to apply to the national surgical population as a whole (slope = 0.0241; R^2 = 0.971). The law applies in all subgroups studied including sex, ASA Physical Status, surgical acuity, surgical severity category, cancer status, and ethnicity (slopes, 0.0066 to 0.0307; R^2, 0.771 to 0.990). Important interactions were found between age, mortality risk, and three high-risk groups (cancer diagnosis, ASA Physical Status IV to V, and high surgical severity).

Conclusions: The Gompertz–Makeham law seems to apply in a national cohort of surgical patients. The inflection point for increased 1-month risk is apparent at age 30 yr. A strict exponential rise in mortality risk occurs thereafter. This finding improves the understanding of surgical risk and suggests a concept-driven approach to improve modeling of age and important interactions in future surgical risk models.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Current postoperative mortality prediction models incorporate patient age using a variety of statistical and biologic assumptions, such as arbitrary age categorizations or mathematical transformations.
- In the nonsurgical general population, epidemiologic research has long shown that mortality risk is relatively constant between ages 18 and 30 yr, and then exponentially rises after age 30 yr. This relationship between age and mortality risk, known as the Gompertz–Makeham law, has not been assessed in the surgical population.

What This Article Tells Us That Is New

- Using a comprehensive registry of 5,615,100 adult patients undergoing surgery between 2007 and 2016 across New Zealand, all-cause mortality within 1 month after surgery occurred in 114,782 (2.0%) patients.
- One-month postoperative risk for patients aged 18 to 30 yr appears constant (slope, –0.0116; R^2, 0.446), while an exponential risk was seen after age 30 yr (slope, 0.0241; R^2, 0.971).
- The Gompertz–Makeham law appears to apply to 1-month surgical mortality and should be considered when including age in surgical mortality modeling.

The biodemography of human aging and characteristic mortality rates associated with increasing age is well described.[1–4] The exponential relationship between chronological age and death rate was first described by Benjamin Gompertz in 1825.[1] William Makeham added an age-independent factor in 1860,[2] and the relationship was subsequently described as the Gompertz–Makeham law of mortality. This age-dependent relationship is apparent in

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multiple human populations,[3,4] where death rate increases exponentially beyond age 30 yr. We will refer to this age-dependent relationship as the Gompertz law and the age-independent relationship as the Makeham law, and the combined relationship as the Gompertz–Makeham law. Figure 1 is a semilogarithmic graph of death rate by chronological age in the New Zealand population from 2012 to 2014 illustrating the Gompertz–Makeham law.[5] The linear pattern beyond 30 yr of age is readily apparent, implying an exponential increase in mortality risk with age (Gompertz law). This has been demonstrated across multiple human populations and is thought to represent how senescence affects mortality.[3,4] Additionally, the near constant mortality risk between 18 and 30 yr demonstrates the age-independent constant component (Makeham law).[3] This constant background component is variable across human populations with little variation in countries with longer life expectancy and more heterogeneity in countries with lower life expectancy,[3,4] and differences are apparent for sex and ethnicity.[5] There is a characteristic U-shaped curve for childhood mortality that will not be discussed further in this article, where we will concentrate on adult patterns of mortality.

Increased risk of perioperative mortality with aging has been reported, but a strict relationship has not been described. In most perioperative risk models, age is a commonly incorporated covariate.[6] The nonlinear relationship between age and perioperative mortality risk means some models use arbitrary age categorizations to accommodate this association. In some multivariable logistic risk models in large populations,[7,8] the logit term for age is modeled as a constant. Increasing perioperative mortality risk with age is well modeled by an exponential relationship in these models. This suggests that perioperative 1-month mortality risk might obey the Gompertz law, but neither modeling approach has discerned a richer age-related pattern. If true, this would define an unexpected relationship not previously described in surgical populations and provide new insights into perioperative mortality risks. Second, it would provide a theoretical basis describing how age should be handled as a covariate in surgical risk models with a baseline risk between 18 and 30 yr and a linear logistic term at age greater than 30 yr. This study aimed to determine whether the Gompertz–Makeham law applies to perioperative mortality risk and the conditions under which it may apply.

Materials and Methods

This article was written adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting cohort studies.[9] Ethical approval for this study (16/CEN/200) was given by the New Zealand National Health and Disability Ethics Committees (Wellington, New Zealand). This was initially a *post hoc* exploratory analysis of the 2-yr dataset used to derive the New Zealand noncardiac surgical RISK tool (NZRISK) surgical mortality tool, a noncardiac surgical mortality tool used widely in clinical pathways in New Zealand. This expanded analysis was written after those initial data were accessed.

Sources of Data

Data from the New Zealand Ministry of Health National Minimum Dataset (NMDS, hereafter referred to as the Dataset)[10] was obtained for participants having surgery between January 1, 2007, and December 31, 2016, inclusive. Mortality data were obtained from a national registry at the Ministry of Health (Wellington, New Zealand)[11] and merged using a unique National Health Identifier. The follow-up period was completed by June 30, 2017.

Participants

Participants were subjects in the Dataset who had been assigned a surgical procedure code including obstetrical surgery and an anesthetic code. Participants who only had local anesthesia as an anesthetic code were excluded. Patients who had multiple procedures during an episode of care had the most complex procedure analyzed as the index procedure. Data were provided from 71 New Zealand public or private hospitals, accounting for more than 99% of all surgical procedures performed with an anesthesiologist present. These included procedures under general, regional, spinal, or epidural anesthesia and local anesthesia with deep sedation in New Zealand.[10]

Outcome

For this study, the outcome was mortality at 30 days as defined by a date of death recorded in the New Zealand mortality register[11] and reported to the Dataset. Outcome assessment was by routine reporting to the Dataset by hospital outcome assessors.

Variables

The exposure was a surgical procedure as listed in the Dataset. Ethnicity was defined by ethnicity codes as reported to the Dataset.[12] All quantitative variables were handled as categorical variables, except age and perioperative mortality risk, which were handled as continuous variables.

Missing Data and Bias

Date of death is a mandatory report in New Zealand. We have assumed that all mortality outcomes have been reported and that there are no missing outcome data. The Dataset is a national registry of all inpatient events reported to the New Zealand Ministry of Health. It captures more than 99% of all surgical procedures performed in New Zealand. The nearly full coverage within this national dataset minimizes bias.

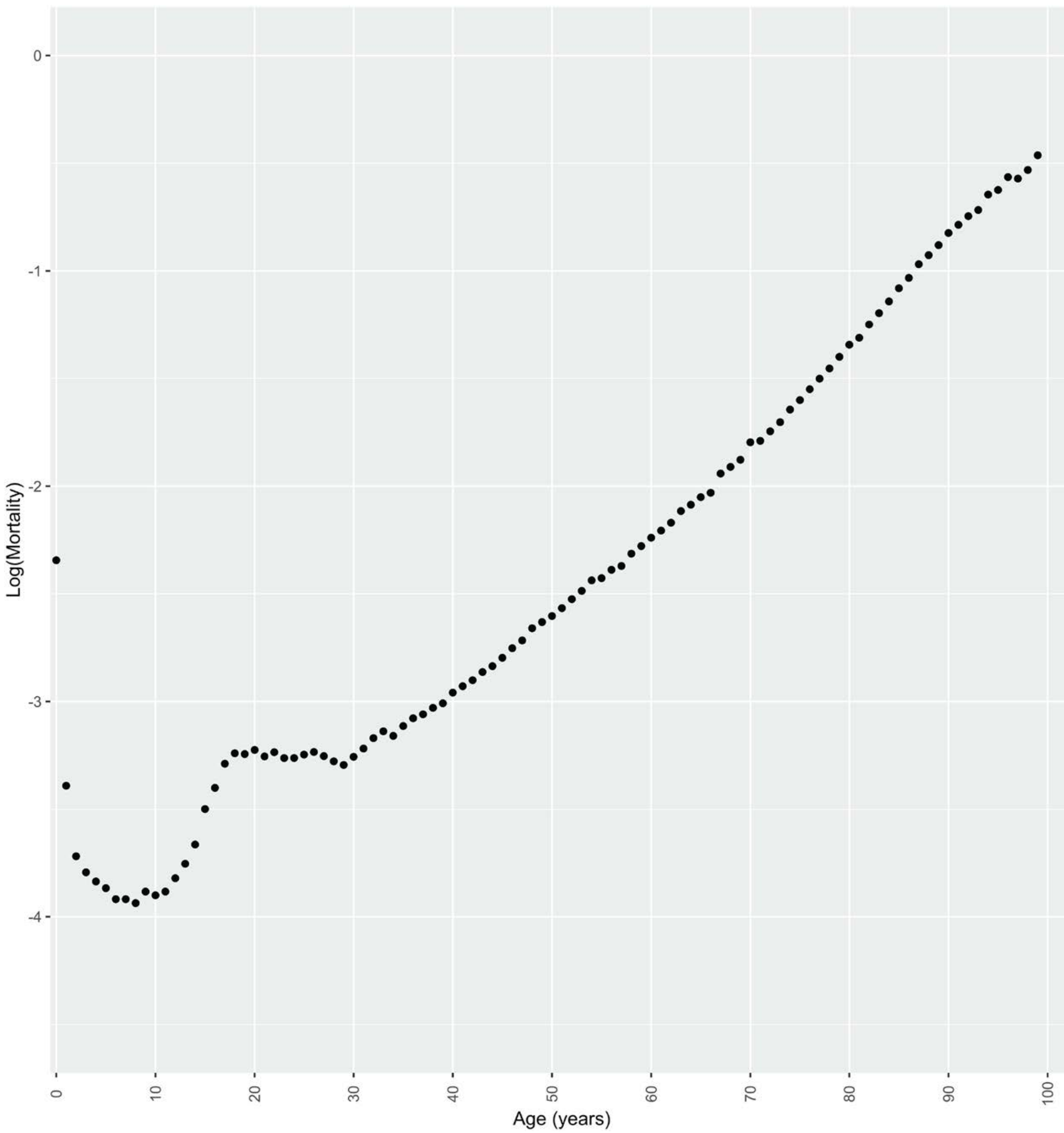

Fig. 1. Semilogarithmic graph of death rate plotted against age in all New Zealand inhabitants, 2012 to 2014. Data from New Zealand Life Tables.[5]

Sample Size

The sample size of 5,615,100 was derived from all patients having surgical procedures in New Zealand in the 10-yr dataset. A 10-yr sampling period was deemed to provide a sample size sufficiently large to provide reliable estimates of perioperative mortality risk in all patient groups within each 1-yr group for the whole dataset or 5-yr cohort within subgroups in the dataset, including the lowest risk categories.

Mathematical and Statistical Analysis

The Gompertz–Makeham law can be summarized where the "force of mortality" or mortality rate at age *t*,

$$\mu(t) = \alpha \text{ x } e^{\beta t} + \gamma$$

where α is a constant, and β is a constant that represents the "actuarial aging rate" or "intrinsic mortality rate" and determines how fast the mortality rate increases with each additional year. The slope of the line above 30 yr in figure 1 is β. The constant γ represents "extrinsic mortality" and represents mortality attributable to hazards in the environment unrelated to biologic age. This mathematical model of the Gompertz–Makeham law was used as the basis for the subsequent statistical analysis.

The primary outcome for the analysis was 1-month perioperative mortality risk and was generated for all surgical patients in cohorts of 1 yr of biologic age for the complete surgical dataset. These data were used to generate a semilogarithmic graph of perioperative mortality risk with increasing age by calculating the $\log_{10}$ estimate of mortality for each single year age cohort. Linear regression models have been fitted using the lm function in R (The R Project for Statistical Computing [r-project.org]; accessed September 2020) to the logarithmic mortality estimates for patient data in the 18- to 30-yr range and greater than 30 yr to allow comparison with the New Zealand general population data (fig. 1). Graphs were prepared in 5-yr cohorts for other categories including sex, American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status, cancer status (clinically significant cancer), surgical acuity (elective or emergency), ethnicity, and surgical severity group (five categories from least invasive to most invasive). More complete descriptions of these categorizations and definitions are provided elsewhere.[7] These categories were prepared to illustrate how the law applies within subgroups. A single linear regression model was fitted for this data from the age of 18 to 30 yr and separately for 30 yr and above as this pattern reproduces the population relationship.[3,4] This simple linear regression model does not incorporate multiple risk factors as in logistic regression. Our modeling philosophy was based on a theory-driven approach. In preliminary work not reported here, we tested alternative data-driven modeling approaches including polynomial splines with fixed and automated knot selection. These data-driven models provided poorer fit, inappropriate knot selection (when automated knot selection used), and inconsistent results that contradicted direct visual inspection. All subsequent modeling reported in this manuscript used the theory-driven, parsimonious model as described.

Results

The primary outcome occurred in 114,782 (2.0%) of 5,615,100 included participants. A semilogarithmic graph of perioperative 1-month mortality risk with increasing age for all patients is presented in figure 2 with lines of best fit for ages 18 to 30 yr and 30 yr and above. A total of 808,598 (14.4%) patients were ages 18 to 30 yr, and 4,806,502 (85.6%) patients were 30 yr and above. Values for slope and the Pearson correlation coefficient are tabulated in table 1.

Graphs of the logarithm of perioperative 1-month mortality risk with increasing age for categories of patients including sex, ASA Physical Status, acuity, cancer status, surgical severity risk categories, and ethnicity are presented in figure 3, A through F.

Discussion

Gompertz Law Applies to Surgical Mortality

The perioperative 1-month mortality risk with increasing age (fig. 2) demonstrates a remarkably similar age-dependent pattern to the population demographic mortality risk age (fig. 1). The Gompertz law appears to apply in a surgical population. Above age 30 yr, there is an excellent linear relationship of logarithm of perioperative 1-month mortality risk and increasing age for the whole 10-yr mortality cohort. A R^2 value of 0.8 is considered excellent, and a value of 1.0 defines a monotonic relationship which $R^2 = 0.971$ approaches. This demonstrates that perioperative mortality risk increases exponentially with age, and therefore, the Gompertz law applies in this national surgical cohort. A close to constant linear relationship of logarithm of perioperative 1-month mortality risk between age 18 and 30 yr is shown. This might mean that modeling perioperative mortality risk as constant between these ages (Makeham law) is a reasonable modeling assumption.

Intrinsic Mortality Rate Is Lower in Some High-risk Categories

When the data are categorized by sex, ASA Physical Status, surgical acuity, cancer status, surgical risk group, and ethnicity, there is a range of slopes, but the tight linear relationship (Gompertz law) remains. The slope of the best fit line represents the intrinsic mortality rate. In particular, the age-related increase in risk is markedly lower in cancer patients compared to patients in whom cancer is not present, as seen in figure 3D. In addition, patients with ASA Physical Status IV to V have a lower slope, as do patients with high surgical severity. This leads us to conclude that senescence-related (age greater than 30 yr) perioperative mortality risk is a less potent risk factor in some higher-risk groups, *e.g.*, cancer, ASA Physical Status IV to V, and major surgical severity. In these populations, the patient's ill health may be an explanation for the observed discrepancy where the associated diagnosis is an additional risk factor which is more important than the underlying risk.

Modeling Age in Surgical Risk Models Should Incorporate Gompertz–Makeham Law

Most current surgical risk calculators incorporate age into the regression model.[6] Often, arbitrary categorizations are used to accommodate the nonlinear association between age and risk.[6] Some risk models based on large datasets such as NZRISK and the PreOperative Score to Predict Postoperative Mortality use linear logit terms in the logistic model, implying an exponential increase in risk with age.[7,8] The National Emergency Laparotomy Audit risk tool[13] uses an alternative data-driven approach to provide

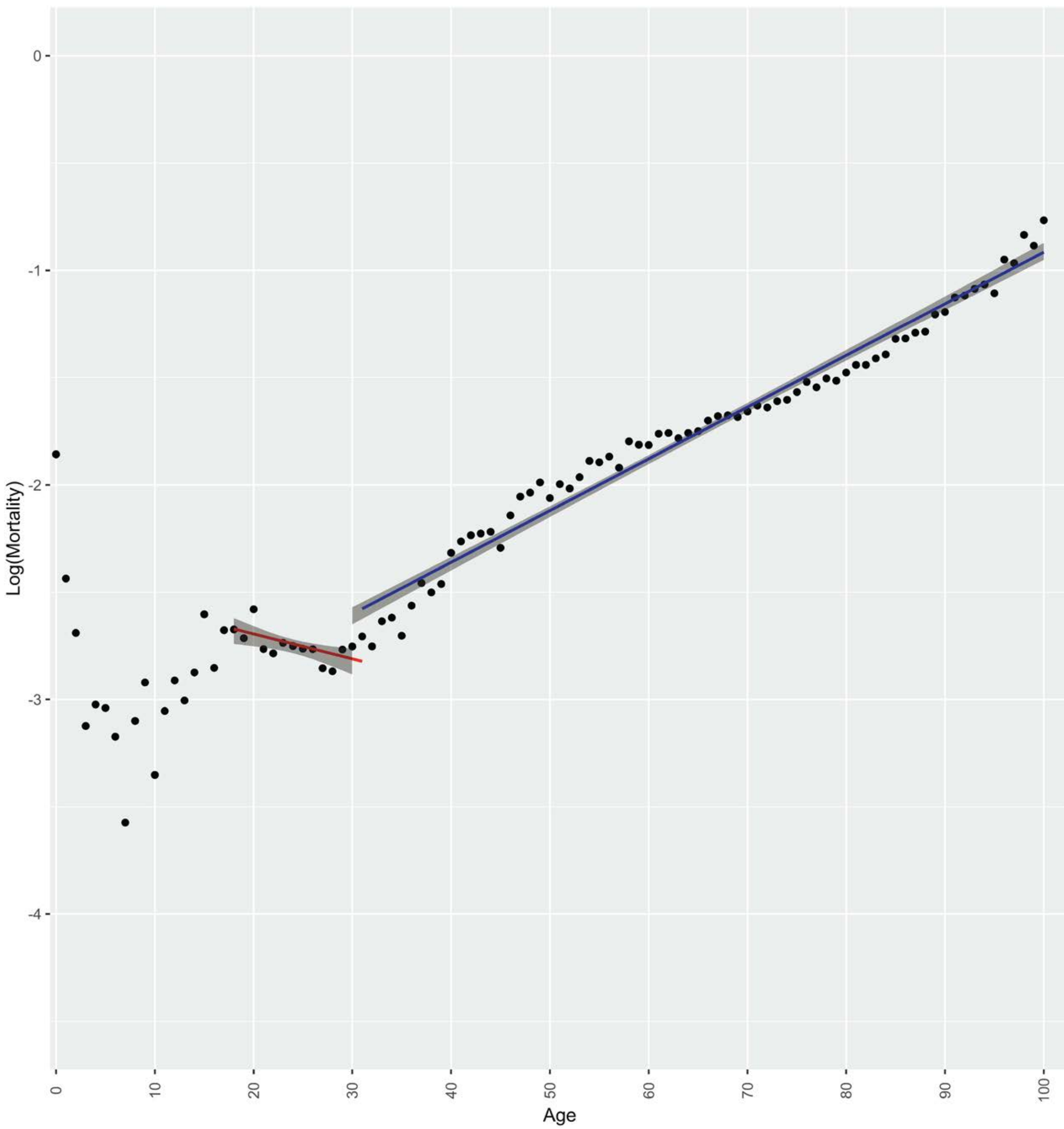

Fig. 2. Graphs of perioperative 1-month mortality risk and with increasing age for all surgical patients in New Zealand, 2007 to 2016, with linear fits from 18 yr to 30 yr and from age 30 yr upward. The *shaded area* represents 95% confidence limits.

relationships and categorizations that are clinically plausible. Machine learning modeling techniques using "big data" will lead to purely data-driven approaches that might incorporate nonlinear relationships.[14,15] How age is handled in these models is based on observed patterns in data and not based on underlying principles, other than clinical experience and intuition. The Gompertz–Makeham law provides an important *a priori* conceptual basis for incorporating age into regression formulae for surgical risk calculators, whereby a baseline risk is used for age 18 to 30 yr and a linear logistic term above age 30 yr. This should provide superior model fit over other choices such as categorization or polynomial splines. This relationship is concept-driven rather than data-driven and provides a robust basis for incorporating age into a risk model. Current surgical risk models would likely be improved by applying modeling principles based on the Gompertz–Makeham law.

Table 1. Slope and Pearson Correlation Coefficient from the Linear Regression Model of Logarithm of 1-Month Perioperative Mortality Risk for Each Category, with Event Rate and Denominator

Category	Slope	R^2	n (%)	Events (% of Events)
Primary analysis			5,615,100	114,782 (2.0)
Age, 18–30 yr	−0.0116	0.446	808,598 (14.4)	2,028 (1.7)
> 30 yr	0.0241	0.971	4,806,502 (85.6)	112,754 (98.2)
Secondary analysis				
Sex, 18–30 yr				
Men, 18–30 yr	0.002	0.0225	292,023 (5.2)	1,219 (1.1)
Women, 18–30 yr	0.016	0.0529	516,575 (9.2)	809 (0.7)
Men, > 30 yr	0.0213	0.987	2,135,076 (38.0)	61,193 (44.9)
Women, > 30 yr	0.0241	0.938	2,671,426 (47.6)	51,561 (53.3)
ASA Physical Status				
I–II, 18–30 yr	0.007	0.919	774,718 (13.8)	598 (0.5)
III, 18–30 yr	−0.001	0.001	30,447 (0.5)	255 (0.2)
IV–V, 18–30 yr	−0.008	0.100	3,433 (<0.1)	1,175 (1.0)
I–II, > 30 yr	0.0307	0.958	3,460,718 (61.6)	6,938 (6.0)
III, > 30 yr	0.0159	0.971	1,224,720 (21.8)	50,320 (43.8)
IV–V, > 30 yr	0.0066	0.810	121,064 (2.2)	55,496 (48.3)
Acuity				
Acute, 18–30 yr	0.015	0.72	258,673 (4.6)	1,651 (1.4)
Elective, 18–30 yr	0.03	0.068	549,925 (9.8)	377 (0.3)
Acute, > 30 yr	0.0216	0.936	1,068,121 (19.0)	85,821 (74.8)
Elective, > 30 yr	0.0243	0.944	3,738,381 (66.7)	26,933 (23.5)
Cancer status				
Not present, 18–30 yr	−0.008	0.261	800,154 (14.2)	1,796 (1.6)
Present, 18–30 yr	0.031	0.91	8,444 (0.2)	233 (0.2)
Not present, > 30 yr	0.0250	0.981	4,371,584 (77.9)	80,822 (70.4)
Present, > 30 yr	0.00709	0.963	434918 (7.7)	31,932 (27.8)
Surgical severity group				
Low, 18–30 yr	−0.03	0.421	481,788 (8.6)	720 (0.6)
Intermediate, 18–30 yr	0.034	0.995	300,078 (5.3)	355 (0.3)
High, 18–30 yr	−0.004	0.118	26,732 (0.5)	953 (0.8)
Low, > 30 yr	0.0301	0.921	2,824,952 (50.3)	35,689 (31.1)
Intermediate, > 30 yr	0.0255	0.990	1,521,014 (27.1)	34,548 (30.1)
High, > 30 yr	0.0142	0.973	460,536 (8.2)	42,517 (37.0)
Ethnicity				
European, 18–30 yr	−0.003	0.031	436,116 (7.8)	1,064 (0.9)
Māori, 18–30 yr	0.03	0.946	195,704 (3.5)	632 (0.6)
Polynesian, 18–30 yr	−0.023	0.052	81,028 (1.4)	111 (0.1)
Other, 18–30 yr	−0.004	0.500	95,750 (1.7)	222 (0.2)
European, > 30 yr	0.0250	0.969	3,505,106 (62.4)	86,153 (75.1)
Māori, > 30 yr	0.0219	0.978	568,186 (10.1)	13,489 (11.8)
Polynesian, > 30 yr	0.0225	0.771	263,894 (4.7)	6,761 (5.9)
Other, > 30 yr	0.0271	0.943	469,316 (8.4)	6,351 (5.5)

ASA, American Society of Anesthesiologists.

Plotting Age and Perioperative Mortality Risk Reliably Identifies Interactions

Plotting graphs of perioperative 1-month mortality risk with increasing age may demonstrate important interactions between age, other risk factors, and perioperative mortality risk. The slope of the relationship is context-dependent, *e.g.*, absence or presence of cancer, ASA Physical Status IV to V, or major surgery. Surgical risk models could incorporate this context-dependent interaction to improve model performance. Currently, the National Emergency Laparotomy Audit surgical risk calculator is one of the few published surgical risk models that incorporate interactions between covariates.[13] It describes the interactions between age and ASA Physical Status, age, and dyspnea, but not age and cancer as demonstrated in this study. However, the nonlinear relationship between age and 1-month mortality in the National Emergency Laparotomy Audit risk tool is modeled with a quadratic fit in the logistic model. The interactions between age and cancer, age and ASA Physical Status, and age and surgical severity described in this study have risk ratios well greater than 2, which is a threshold considered large enough to infer interactions that are considered important.[16,17] The associations with an underlying biologic law, *e.g.*, the Gompertz–Makeham law, make the discovery of these interactions more plausible[18] and are likely to be reliable in New Zealand patients but require replication

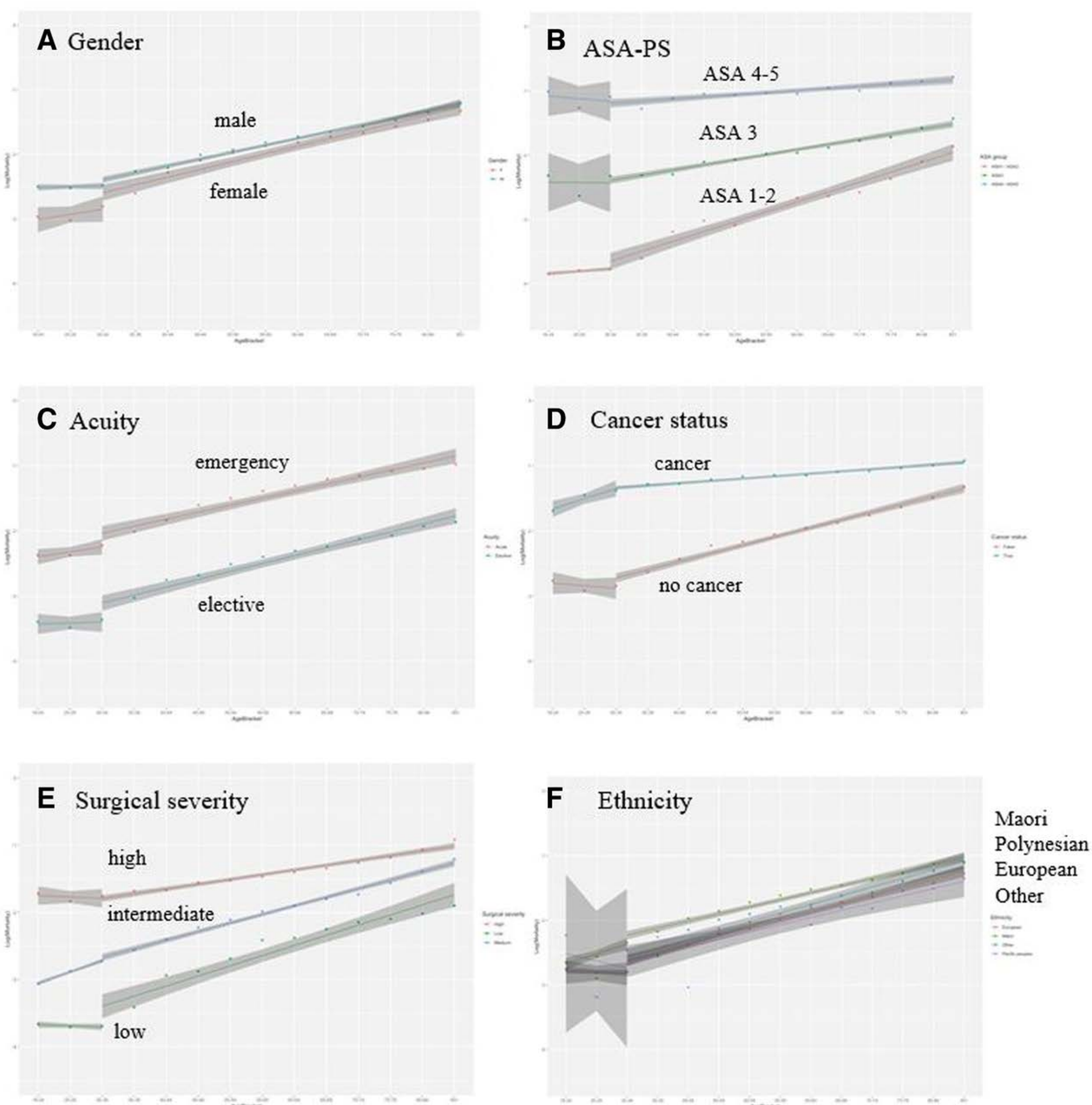

Fig. 3. Graphs of perioperative 1-month mortality risk with increasing age for patients in categories of biologic sex (*A*), American Society of Anesthesiologists (ASA) Physical Status (PS; *B*), surgical acuity (*C*), cancer status (*D*), surgical severity (*E*), and ethnicity (*F*), for surgical patients in New Zealand, 2007 to 2016.

in other international datasets. If replicated in other datasets, these interactions will result in overestimation of perioperative risk in patients with cancer, ASA Physical Status IV to V, and major surgery with the overestimation greatest in elderly patients. Many risk models overestimate risk in higher risk bands,[6,19,20] and these interactions may provide an explanation for predictive inaccuracy in higher risk groups. The Gompertz–Makeham law provides a theoretical basis to search for interactions and calculate their magnitude and statistical significance. Plotting the relationship between age, mortality risk, and important covariates provides a method to assess the strength and robustness of the interaction. This should give users of risk models increased confidence in the face validity of the model, as opposed to models for which model choices are not explained as in machine learning models. The presence of interactions may be dependent on the model derivation population, and whether the interactions are statistical or biologic in origin requires further research.

Strengths and Weaknesses

Weaknesses of this study include that the results are derived from a single national dataset and may not be generalizable internationally. Low event rates in patients aged 18 to 30 yr mean inferences related to the Makeham law in this surgical cohort are limited due to low event rates and insufficient data to test this association reliably. In addition, the clinical significance of the slope and R^2 values observed in our analyses (table 1) is difficult to establish. Strengths of this study are the description of a previously undescribed relationship for surgical mortality with similar relationships being well described in multiple demographic populations. The sample size of 5,615,100 allows reliable modeling, especially when applying the Gompertz law for patients aged greater than 30 yr. Sound modeling decisions are fundamental in deriving reliable, accurate risk tools.[21] This improved approach to modeling age as a covariate and associated interactions has been incorporated into an updated versions of NZRISK with publication and website upgrade expected late 2024.

Conclusions

We have shown (1) that the Gompertz–Makeham law applies in a 10-yr cohort of all surgical patients in New Zealand, and (2) that the Gompertz law applies, but age-dependent increase in risk is lowest in patients who have cancer, undergo major surgery, and have ASA Physical Status IV to V due to the interaction with age, perioperative mortality, and each of these risk factors. Future surgical risk models would benefit from this concept-driven approach rather than a data-driven approach and incorporate age as a covariate based on the Gompertz–Makeham law. These findings need to be replicated, and the implications to our understanding of the epidemiology of perioperative mortality require further exploration.

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Competing Interests

Dr. Boyle received a Ph.D. stipend from Precision Driven Health (Auckland, New Zealand), a research funding organization. Precision Driven Health is a research collaboration between the New Zealand Ministry of Health (Wellington, New Zealand), district health boards, New Zealand universities, and Orion Health (Auckland, New Zealand; vendors of a "health data platform"). Dr. Boyle was previously an employee of Orion Health and was employed by them on completion of his Ph.D. D. Campbell has performed funded research for Route 92. Dr. Short has performed funded research for Beckton Dickinson and Roche Pharmaceuticals. The other authors declare no competing interests.

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