ANESTHESIOLOGY

Complications as a Mediator of the Perioperative Frailty–Mortality Association

Mediation Analysis of a Retrospective Cohort

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ABSTRACT

Background: Preoperative frailty is strongly associated with postoperative complications and mortality. However, the pathways between frailty, postoperative complications, and mortality are poorly described. The authors hypothesized that the occurrence of postoperative complications would mediate a substantial proportion of the total effect of frailty on mortality after elective noncardiac surgery.

Methods: Following protocol registration, the authors conducted a retrospective cohort study of intermediate- to high-risk elective noncardiac surgery patients (2016) using National Surgical Quality Improvement Program data. The authors conducted Bayesian mediation analysis of the relationship between preoperative frailty (exposure, using the Risk Analysis Index), serious complications (mediator), and 30-day mortality (outcome), comprehensively adjusting for confounders. The authors estimated the total effect of frailty on mortality (composed of the indirect effect mediated by complications and the remaining direct effect of frailty) and estimated the proportion of the frailty–mortality association mediated by complications.

Results: The authors identified 205,051 patients; 1,474 (0.7%) died. Complications occurred in 20,211 (9.9%). A 2 SD increase in frailty score resulted in a total association with mortality equal to an odds ratio of 3.79 (95% credible interval, 2.48 to 5.64), resulting from a direct association (odds ratio, 1.76; 95% credible interval, 1.34 to 2.30) and an indirect association mediated by complications (odds ratio, 2.15; 95% credible interval, 1.58 to 2.96). Complications mediated 57.3% (95% credible interval, 40.8 to 73.8) of the frailty–mortality association. Cardiopulmonary complications were the strongest mediators among complication subtypes.

Conclusions: Complications mediate more than half of the association between frailty and postoperative mortality in elective noncardiac surgery.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Moderate-to-severe complications are common after major surgery and can have substantial impacts on long-term outcomes
- Preoperative frailty is strongly associated with postoperative complications and mortality

What This Article Tells Us That Is New

- In a retrospective cohort study of intermediate- to high-risk elective noncardiac surgery patients, complications mediated over half of the association between frailty and postoperative mortality
- Cardiopulmonary complications contributed to this association with a higher probability than renal or infectious events

Moderate to severe complications are common after major surgery (15 to 35% incidence)[1,2] and can have substantial impacts on long-term outcomes. People who experience a serious complication are more likely to die and have an approximately fivefold increase in healthcare resource consumption after surgery compared to people who navigate the perioperative period complication-free.[1,3]

Risk factors for postoperative complications are well studied and include demographic factors (*e.g.*, age and sex), surgical factors (procedure, approach, and duration), and patient factors (acute and chronic illness).[4–6] Advanced age is strongly associated with the risk of postoperative complications; however, among older people, rates of complications range substantially.[7] This variation in complication risk is partly explained by the presence of frailty, a multidimensional syndrome related to the accumulation of age- and disease-related deficits.[8,9] A recent systematic review found the presence of preoperative frailty to be the strongest significant risk factor for complications in older surgical patients,[5] and multiple reviews demonstrate that frailty is associated with at least a twofold increase in postoperative mortality.[8,10,11] Initial evidence suggests a potential pathway

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between frailty, complications, and mortality whereby older people with higher levels of frailty are more likely to experience a complication after surgery and are more likely to die as a result of their complication (a phenomenon referred to as "failure to rescue").[12,13]

A complication-mediated pathway (*i.e.*, failure to rescue) would represent an indirect pathway from frailty to postoperative mortality (fig. 1). Previous studies demonstrate that medical and surgical complications underlie approximately two thirds of in-hospital deaths after surgery, meaning that one in three deaths occur in a non–complication-mediated manner. For people with frailty, who are at greater risk of mortality regardless of having surgery, direct (*i.e.*, non–complication-mediated) pathways may also be of greater relevance, because chronic conditions, such as dementia and cancer, are more common as causes of death when frailty is present.[14] The presence of frailty is associated with increased utilization of palliative care services, further highlighting the possibility of unique pathways to mortality in people with higher degrees of frailty. Furthermore, given the physiologic vulnerability inherent in having frailty, it is also possible that the stress of surgery itself could result in postoperative death for people with frailty without necessarily causing a clinically significant end organ complication.

Understanding the degree to which complications may mediate the association between frailty and postoperative mortality could inform development of interventions and processes of care that are urgently needed to improve outcomes for surgical patients with frailty. If complications mediate a substantial proportion of the effect of frailty on postoperative mortality, then prevention and treatment of complications would emerge as a clear priority for clinicians and researchers. In contrast, if complications do not mediate a substantial proportion of mortality risk, then other strategies to improve outcomes would be required. Therefore, we undertook a retrospective cohort study using prospectively collected surgical registry data to perform mediation analysis to estimate the degree to which complications mediate the association between frailty and postoperative mortality in noncardiac surgery. We hypothesized that the occurrence of postoperative complications would mediate a substantial proportion of the total effect of frailty on mortality after elective noncardiac surgery.

Materials and Methods

Design and Data Source

We used prospectively collected data from the National Surgical Quality Improvement Program (NSQIP) participant use file to conduct a retrospective cohort study. Trained surgical clinical reviewers at each participating hospital collect NSQIP data using standardized definitions and techniques, supported by local and central quality checks to ensure data integrity.[15] Ethical approval was granted (Ottawa Health Sciences Network Research Ethics Board [Ottawa, Canada] approval No. 20160439-01H). A protocol was prespecified and registered at the Center for Open Science (https://osf.io/suq6r/; accessed January 20, 2021), informed by methodologic guidelines for mediation and Bayesian analysis.[16,17] Reporting followed the

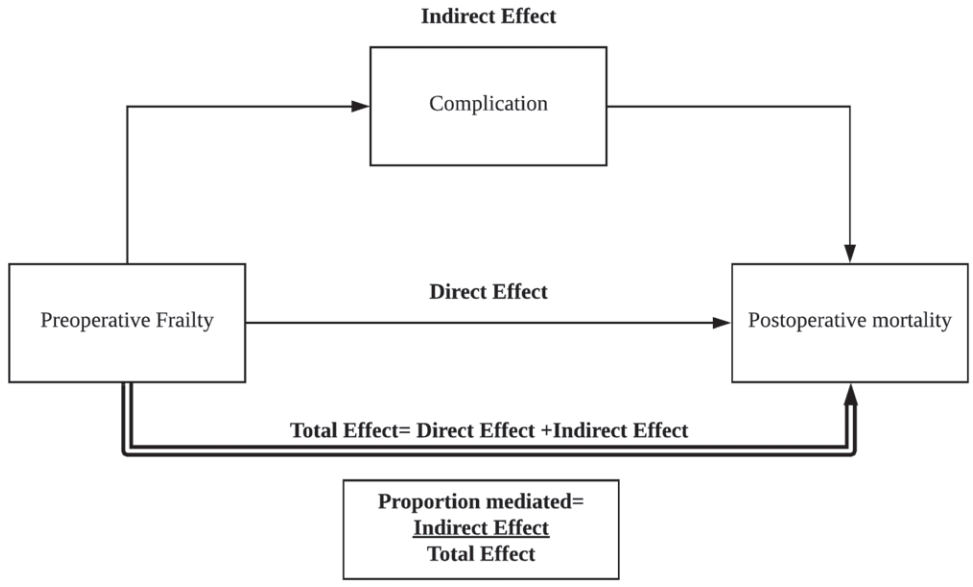

Fig. 1. Proposed pathways between preoperative frailty and postoperative mortality, mediated by complications. Also included are descriptors of the key aspects of mediation, including the total effect of frailty on mortality, which is composed of the indirect effect mediated by complications and the direct effect attributable to frailty independent of the mediation pathway.

STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement[18] and the Reporting Of Bayes Used in clinical STudies (ROBUST) criteria.[19]

Cohorts

We studied adults having elective intermediate- to high-risk noncardiac surgery in 2016, using a cohort definition validated by Liu *et al.*[20] We then performed an "internal–external" validation to explore whether results were consistent in a bowel surgery cohort of mixed urgency; this cohort was identified because it was less procedurally diverse and temporally separated (2010 to 2015) from the initial cohort.[21] Both cohorts were defined using relevant current procedural terminology codes (Supplemental Digital Content 1, table S1, http://links.lww.com/ALN/C537).

Exposure

We identified preoperative frailty in each participant using the Risk Analysis Index–Administrative, a multidimensional frailty score that is patterned after the Minimum Data Set Mortality Risk Index–Revised, calculated using the methods described and validated by Hall *et al.*[22] Although several approaches to frailty assessment have been described in NSQIP data, the Risk Analysis Index–Administrative is the only instrument consistent with a multidimensional assessment of frailty and has recently been shown to have higher predictive validity than the NSQIP five-item frailty index, as well as added predictive value beyond the variables already included in the NSQIP Universal Risk Calculator.[23] The Risk Analysis Index–Administrative is a continuous variable with a range from 0 to 81, with higher scores indicating greater frailty. The Risk Analysis Index–Administrative score is based on a standard scoring system (Supplemental Digital Content 1, table S2, http://links.lww.com/ALN/C537) that encompasses age, sex, cancer, weight loss, renal failure, heart failure, poor appetite, dyspnea, living status, and functional independence.

Mediators

Our proposed mediator was the occurrence of a serious complication (based on the definition used by the NSQIP Risk Calculator[24]). Any individual who experienced one or more of the following within 30 days was assigned a serious complication as a binary variable: cardiac arrest, myocardial infarction, pneumonia, progressive renal insufficiency, acute renal failure, pulmonary embolism, deep vein thrombosis, return to the operating room, deep incisional surgical site infection, organ space surgical site infection, systemic sepsis, unplanned intubation, urinary tract infection, and wound disruption. As described in Supplemental Digital Content 1, table S3 (http://links.lww.com/ALN/C537; including NSQIP-specific definitions for each complication), complications are identified by trained reviewers using standardized definitions.

Untangling the role of different complication subtypes is challenging, because individuals could experience multiple complications and subtypes. Therefore, we created groups of complication subtypes: cardiopulmonary (cardiac arrest, myocardial infarction, pneumonia, pulmonary embolism, deep vein thrombosis, unplanned intubation), infectious (pneumonia, deep incisional surgical site infection, organ space surgical site infection, urinary tract infection, systemic sepsis), or renal (progressive renal insufficiency, acute renal failure) to assess the extent that these groupings acted as mediators. These subtypes were coded in two ways: (1) any occurrence of a subtype complication, whereby an individual who experienced more than one type of complication would be included in each subtype, and (2) isolated occurrence of a complication subtype, whereby anyone experiencing more than one complication was excluded, leaving no cooccurrence between subtypes (*i.e.*, only individuals who experienced a single complication of a single subtype were coded and analyzed, with pneumonia residing only in the cardiopulmonary subtype).

Outcome

The primary outcome was all-cause mortality within 30 days of the index surgery.

Statistical Analyses

All analyses were performed using the R statistical language (R Foundation for Statistical Computing, Vienna, Austria). We used the brms package to create mediation models[25] and the mediation function in the sjstats package to calculate direct and indirect effects. Cohort characteristics were evaluated in people with and without a frailty score greater than 15 using absolute standardized differences.[22,26]

Our overall analytic approach involved use of Bayesian modeling, because this allowed us to calculate appropriate credible intervals to gauge uncertainty around our estimates using Markov chain Monte Carlo simulations. A credible interval can be interpreted as the range within which there is a 95% probability of finding the true value given the data analyzed and previous knowledge.[27] We used highest density intervals (where all points in the interval have higher probability density than points outside the interval but can be asymmetric around the median), as opposed to equal tailed intervals (which are symmetric, based on the 2.5th and 97.5th percentile, but can contain lower probability densities inside than outside of the interval). As we lacked in-depth previous knowledge of anticipated mediation effects, we used weakly informative priors (Supplemental Digital Content 1, table S4, http://links.lww.com/ALN/C537), as recommended, which decreases the likelihood of estimating unrealistically large or small effects, without having a substantive effect on regression parameters.[28] The specific distribution used for fixed effects was a Student *t* distribution with 3 degrees of freedom, mean of 0, and scale

of 2.5, which has been shown to outperform weakly informative priors based on the normal distribution because the thicker tails of the *t* distribution allow for occasional estimation of larger coefficients.[28] Default priors in brms were used for random intercepts, which were also weakly informative, based on a half Student *t* distribution with 3 degrees of freedom and a scale parameter that derived from the SD of the response after applying the logit link function. We also tested the potential impact of previous distribution choice by subsequently using a normal prior for frailty (both predicting complications and mortality) based on the normal distribution with a mean of 0.405 (equal to an odds ratio or 1.5, a conservative but typical effect size for frailty in perioperative studies).[8] We used default settings for brms (1,000 warmup and 2,000 sampling iterations) and increased iterations as required if chains did not adequately converge. Adequate mixing of chains and autocorrelation were evaluated using visual plots, effective sample size estimates (*i.e.*, an estimation of the amount of independent information contained within the Markov chains,[29] for which larger values are better and values greater than 1,000 are typically considered sufficient[25]), and Geweke diagnostics for chain convergence.

Mediation analyses require strong control for confounders[17]; therefore, our primary approach was to build models that included the Risk Analysis Index–Administrative plus adjustment for all variables in the NSQIP Risk Calculator (parameterizations are listed in Supplemental Digital Content 1, table S5, http://links.lww.com/ALN/C537) adjusting for each procedure using a random intercept. All variables were standardized to have a mean of 0 and a SD of 0.5, allowing priors to be appropriately scaled for all covariates. This meant that effect sizes for the continuous frailty score represented a change in 12 points (*e.g.*, from 0 to 12, which is similar to the typical cutpoint of 15 for the Risk Analysis Index–Administrative[22]).

To conduct a mediation analysis, two regression models must be created in a multivariate framework (*i.e.*, with more than one dependent variable)[17]; in our case, both were logistic models because our outcome and mediator were dichotomous. The first regression model had the outcome (mortality) as the dependent variable; the primary exposure (frailty), mediator (complications), and covariates (NSQIP Risk Calculator variables) were predictors. The second model had the mediator as the dependent variable with the exposure and covariates as predictors. From these models, we calculated the *direct effect* of frailty on mortality (odds ratio for frailty from the model predicting mortality, because this odds ratio is also adjusted for the mediator effect), the *indirect effect* (which is the product of regression coefficient associating frailty with complications from the second model and regression coefficient associating complications with mortality from the first model), and the *total effect* (which is the sum of the direct and indirect effects) of frailty on mortality. The proportion of the effect mediated by complications was then calculated as the indirect effect divided by the total effect, which was estimated using the median of the posterior distribution accompanied by a 95% credible interval that reflected the highest density interval across posterior distributions.

Sensitivity Analyses

We reran our primary analysis in an internal–external validation cohort of mixed urgency bowel surgery (2010 to 2015) to test the generalizability of our findings. Next, we focused on evaluating the mediation pathway in greater detail by estimating the impact of different complication subtypes. The first approach used a broad definition of subtypes; we ran three versions of the primary mediation model, and each complication subtype defined using any occurrence (*i.e.*, allowing multiple occurrences and possible overlap) was entered sequentially as the mediator variable. Comparison of the strength of evidence that one complication type was more likely to mediate the frailty–mortality association was quantified using Bayes factors (guide to interpreting strength of evidence using Bayes factors in Supplemental Digital Content 1, table S6, http://links.lww.com/ALN/C537).[30] Many patients may experience multiple complications and complication types, which could obscure the specific subtype mediation pathway. Therefore, we conducted a second approach using isolated complication subtypes. People who experienced more than one serious complication were excluded, which allowed us to more accurately define the role of each subtype in a single multivariate model (*i.e.*, a single regression framework that allowed posterior distributions to be directly compared across complication subtype mediators). This model included each isolated complication subtype as a dependent variable (each adjusted separately for confounders), as well as the mortality model with each subtype as a predictor, allowing estimation of the joint effects of each subtype. Of note, where the mediation analyses considered multiple mediators, the sum of mediation proportion point estimates (in our case, the median of the posterior distribution) could exceed 1; therefore, relative effect sizes should be considered instead of absolute values.[31,32] Following peer review recommendations, we further explored whether mediation may differ by case mix by rerunning our primary analysis limited to general surgery cases in our elective high-risk cohort only.

Sample Size and Missing Data

Samples sizes were based on all available cases in the NSQIP participant use file meeting inclusion criteria for our two cohorts. No variables had missing values, but some were listed as unknown: functional status (n = 823 [0.4%], where these values were collapsed with the independent category); American Society of Anesthesiologists (ASA; Schaumburg, Illinois) score (n = 330 [0.2%], where these values were

collapsed with the ASA II category); and transfer status (n = 103 [less than 0.1%], where these values were collapsed with the not transferred category).

Results

We identified 205,051 patients having elective intermediate- to high-risk noncardiac surgery. The mean ± SD Risk Analysis Index–Administrative score was 6 ± 5. Cohort demographics separated by Risk Analysis Index–Administrative score cutoff of 15 are presented in table 1; most characteristics differed by Risk Analysis Index–Administrative score, with higher score patients being older, more functionally dependent, and more likely to have acute and chronic medical conditions.

Outcome Rates

Within 30 days of surgery, 1,474 (0.7%) people died, and 20,211 individuals (9.9%) experienced a serious complication. Of those who died, 1,028 (69.7%) suffered a complication before dying. Among those who experienced a complication, 13,481 (66.7%) had a single serious complication. Complication subtypes included 6,927 (3.4%) cardiopulmonary, 10,654 (5.2%) infectious, and 1,272 (0.6%) renal events. Overlaps of complication subtypes are reported in Supplemental Digital Content 1, table S7 (http://links.lww.com/ALN/C537).

Mediation

All models converged, had adequate effective sample size, and did not suffer from substantive autocorrelation (model diagnostics and a model summary are provided in Supplemental Digital Content 1, table S8, http://links.lww.com/ALN/C537). The general surgery sensitivity analysis required 5,000 sampling iterations to achieve adequate effective sample size. Figure 2 provides the posterior distributions and 95% and 50% credible intervals for the direct, indirect, and total effects of frailty on mortality. The total effect of a 12-point greater frailty score was 3.79-fold greater odds of mortality (95% credible interval, 2.48 to 5.64), which resulted from a direct effect attributable to frailty (odds ratio, 1.76; 95% credible interval, 1.34 to 2.30) and an indirect effect mediated by complications (odds ratio, 2.15; 95% credible interval, 1.58 to 2.96). This resulted in a proportion of the effect of frailty on mortality mediated by complications of 57.3% (95% credible interval, 40.8 to 73.8). The estimated probabilities that the mediation effect was greater than 0% (*i.e.*, a nonnull mediation effect), 10%, 33%, and 50% are provided in table 2.

When using an informative, normal previous distribution, the total effect of a 12-point greater frailty score was 3.74-fold greater odds of mortality (95% credible interval, 2.43 to 5.45), which resulted from a direct effect attributable to frailty (odds ratio 1.73, 95% credible interval, 1.31 to 2.29) and an indirect effect mediated by complications (odds ratio 2.14, 95% credible interval, 1.58 to 2.92). This resulted in a proportion of the effect of frailty on mortality mediated by complications of 58.0% (95% credible interval, 41.1 to 73.9).

Table 1. Demographics Grouped by High and Low Frailty Scores

Characteristic	Frailty Score ≤ 15 (n = 195,034)	Frailty Score > 15 (n = 10,017)	Standardized Difference
Female	95,823 (49.1)	4,607 (46.0)	0.06
Diabetes mellitus	35,138 (18)	2,051 (20.5)	0.06
Hypertension	107,873 (55.3)	5,046 (50.4)	0.10
Heart failure	1,053 (0.5)	269 (2.7)	0.18
Dyspnea at rest	487 (0.3)	322 (3.2)	0.22
Moderate dyspnea	12,130 (6.2)	762 (7.6)	0.06
Smoker	37,450 (19.2)	1,665 (16.6)	0.07
COPD	10,920 (5.6)	763 (7.6)	0.08
Dialysis	1,430 (0.7)	367 (3.7)	0.21
Acute kidney injury	217 (0.1)	80 (0.8)	0.10
Metastatic cancer	278 (0.1)	7,890 (78.8)	2.71
Preoperative ventilation	29 (0.0)	22 (0.2)	0.06
Systemic inflammatory response syndrome	1,081 (0.6)	187 (1.9)	0.12
Sepsis	391 (0.2)	82 (0.8)	0.09
Septic shock	17 (0.0)	13 (0.1)	0.04
Ascites	260 (0.1)	199 (2.0)	0.19
Steroid	9,431 (4.8)	717 (7.2)	0.10
Partially dependent	2,564 (1.3)	1,267 (12.7)	0.46
Totally dependent	0 (0.0)	532 (5.3)	0.33
ASA physical status			
I or II	77,433 (42.1)	2,026 (20.7)	0.47
III	102,304 (52.5)	6,572 (65.6)	0.27
IV	10,517 (5.4)	1,361 (13.6)	0.28
V	24 (0.0)	6 (0.1)	0.04
Age			
< 65 yr	104,817 (53.7)	5,283 (52.7)	0.02
65 to 74 yr	57,721 (29.6)	2,537 (25.3)	0.10
75 to 84 yr	27,942 (14.3)	1,842 (18.4)	0.11
85+ yr	4,563 (2.3)	355 (3.5)	0.07
General surgery	74,450 (38.2)	6,276 (62.7)	0.51
Gynecology	3,748 (1.9)	521 (5.2)	0.18
Neurosurgery	20,747 (10.6)	751 (7.5)	0.11
Orthopedics	50,158 (25.7)	632 (6.3)	0.55
Otolaryngology	822 (0.4)	71 (0.7)	0.04
Plastic surgery	1,796 (0.9)	70 (0.7)	0.02
Thoracis surgery	3,637 (1.9)	264 (2.6)	0.05
Urology	18,778 (9.6)	638 (6.4)	0.12
Vascular surgery	20,898 (10.7)	794 (7.9)	0.10

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

Internal–External Validation

Among people having bowel surgery from 2010 to 2015, the total, direct, and indirect effects of frailty were attenuated compared to the mixed noncardiac cohort (total frailty–mortality odds ratio, 1.84; 95% credible interval, 1.60 to 2.12; direct odds ratio, 1.61; 95% credible interval, 1.44 to 1.82; indirect odds ratio, 1.14; 95% credible interval, 1.06 to 1.23), as was the proportion mediated (21.2%; 95% credible

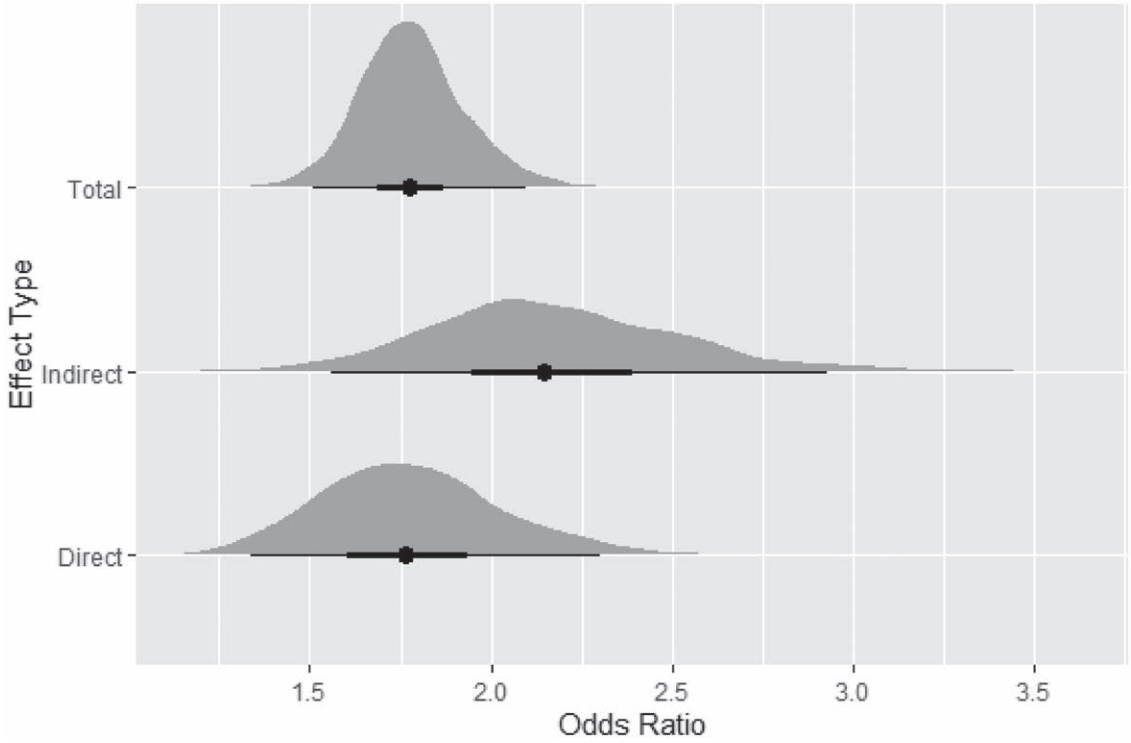

Fig. 2. Total, direct, and indirect effects of frailty on mortality, expressed as odds ratios. Included are posterior distributions for each parameter, along with a *dot* (representing the median value), a *thick bar* (50% credible interval), and *thin bar* (95% credible interval). Credible intervals were based on the highest density interval of the posterior distribution.

Table 2. Probability of Different Proportion of the Frailty–Mortality Association Mediated by Complications

	Probability of Mediation Proportion, %			
Cohort	**> 0**	**> 10**	**> 33**	**> 50**
Elective intermediate- to high-risk noncardiac surgery	> 99	> 99	> 99	83
Bowel surgery	> 99	98	0	0

Probabilities were calculated from posterior distributions of causal mediation models adjusted for National Surgical Quality Improvement Program Risk Calculator variables using weakly informative priors.

interval, 10.5 to 31.9). The estimated probabilities that the mediation effect was greater than 0%, 10%, 33%, and 50% are provided in table 2.

A sensitivity analysis limited to general surgery cases was similar to the primary findings (total frailty–mortality odds ratio, 3.19; 95% credible interval, 2.03 to 5.10; direct odds ratio, 1.73; 95% credible interval, 1.26 to 2.34; indirect odds ratio, 1.84; 95% credible interval, 1.31 to 2.56; proportion mediated, 52.8%; 95% credible interval, 31.5 to 73.7).

Sensitivity Analyses by Complication Type

The probability of nonzero mediation, and related Bayes factors, by subtype, are reported in table 3. Posterior distributions and credible intervals estimating the proportion of the frailty–mortality association mediated by isolated complication subtype are provided in figure 3. The median estimates of the proportion of the frailty–mortality association mediated by renal and cardiopulmonary complications were similar (71.2% *vs.* 64.5%); however, only the 95% credible interval for cardiopulmonary complications excluded the null value (*i.e.*, 0). There was minimal evidence that infectious complications mediated a substantial proportion of the frailty–mortality association.

Discussion

In a retrospective analysis of prospectively collected surgical registry data, we estimate that complications may mediate over half of the association between frailty and postoperative mortality in elective noncardiac surgery patients. Cardiopulmonary complications may contribute to this association with a higher probability than renal or infectious events. The extent of mediation may vary by surgery type and urgency, as a smaller proportion of the frailty–mortality

Table 3. Posterior Probabilities and Bayes Factors for Non-zero Mediation Effects by Complication Subtype

Complication Subtype Definition	Probability > 0 Effect, %	Bayes Factor*
Any occurrence		
Renal	94	16
Infectious	99	999
Cardiopulmonary	99	1,332
Isolated occurrence†		
Renal	89	8
Infectious	22	0.28
Cardiopulmonary	99	69

All analyses were adjusted for NSQIP Risk Calculator variables and used weakly informative priors.

*Bayes factors represent the relative strength of evidence for two scenarios. In this case, the Bayes factor is the ratio of the probability that the complication subtype has a nonzero mediation effect divided by the probability that the complication subtype has no mediation effect. A value of 1 would mean equivalent evidence, more than 1 is evidence that there is a mediation effect, and less than 1 is evidence of no mediation effect. †Isolated occurrence analyses were limited to participants who experienced one or more serious complications only using multivariate models containing all subtypes.

association was mediated by complications in a mixed urgency bowel surgery cohort. Therefore, as new frailty-focused interventions are developed, clinicians and researchers should consider strategies to reduce complication rates and treat their occurrence, while also considering the needs of the 40% of frailty-related deaths that may occur *via* pathways not associated with complications.

Numerous systematic reviews report strong and consistent associations between higher levels of preoperative frailty and higher postoperative mortality rates, findings that are apparent across surgical specialities and different approaches to frailty assessment.[8,10,11] Similarly, systematic reviews document substantially higher rates of postoperative complications when frailty is present before surgery.[5] However, limited data exist that explore pathways between frailty, complications, and postoperative mortality, a knowledge gap that may contribute to the continued shortage of evidence-based interventions to improve outcomes for surgical patients with frailty.[33]

Previous studies have investigated the association of frailty with failure to rescue, and document that frailty is

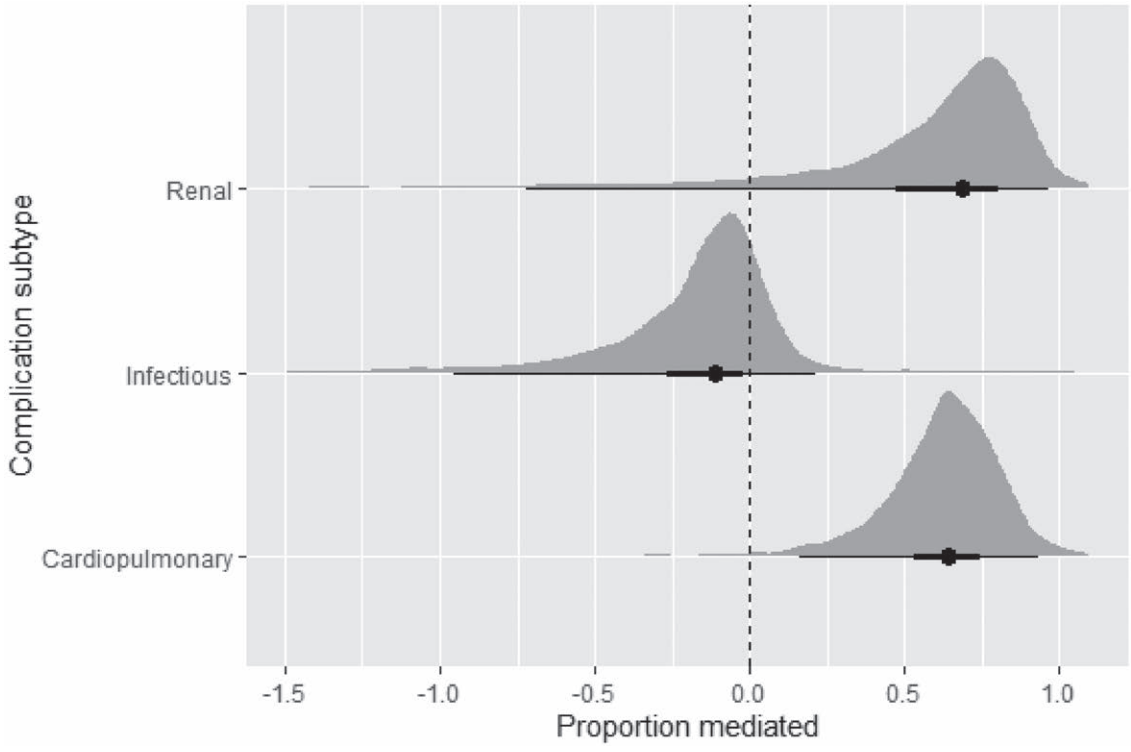

Fig. 3. Proportion of the effect of frailty on mortality mediated by different complication subtype definitions. Included are posterior distributions for each parameter, along with a *dot* (representing the median value), a *thick bar* (50% credible interval), and *thin bar* (95% credible interval). Credible intervals were based on the highest density interval of the posterior distribution. Because multiple mediators were included in this analysis, the values should be interpreted as relative strengths, not absolute values (as medians can, and do, sum to greater than 1). The *dashed vertical line* is the null value; therefore, credible intervals overlapping this line are less than 95% probable to mediate an effect.

associated with a 2.5- to 5-fold greater odds of dying after experiencing a postoperative complication in high-risk, emergency, and trauma surgery.[12,34,35] Frailty is also associated with failure to rescue in a dose–response fashion,[12] further supporting a possible relationship. However, these findings address only a single component of the proposed pathway between frailty and mortality. Our findings build on these results by considering both the direct effect of frailty on mortality and the indirect effect of complications that we hypothesized may mediate a substantial proportion of the observed frailty–mortality association. This allowed us to document not only what happened after a complication, conditional on frailty status, but also the extent to which the adverse association between frailty and mortality may have operated *via* a complication-dependent pathway. In doing so, we found that over half of the association of frailty with postoperative mortality appears to be mediated by the occurrence of postoperative complications, even controlling for other possible sources of confounding. Based on our data, the likelihood of this relationship being nonnull was very high (greater than 99% probability that over 33% of the observed total effect was complication-mediated, and 83% probability that over 50% of the total effect was mediated by complications). However, this also suggests that a substantial proportion of frailty-associated postoperative mortality may be related to non–complication-mediated mechanisms, which is higher than previous estimates in non–frailty-focused studies.[36]

Our finding that the frailty–mortality association was substantially mediated by complications, in particular cardiopulmonary complications, is consistent with the existing perioperative frailty literature. First, people with frailty are inherently vulnerable to stressors.[37,38] Surgery results in substantial physical and physiologic stress,[39] stress that can directly lead to end-organ damage in individuals with limited preoperative reserve.[40] Previous studies report that people with frailty die at a much higher rate immediately after elective and emergency surgery than people without frailty,[41,42] and that inadequate cardiovascular reserve during surgery may mediate up to 10% of the association between frailty and postoperative mortality.[43] Furthermore, among people who experience a postoperative cardiovascular complication, frailty characteristics (advanced age, higher comorbidity burden, and higher ASA score) are the strongest predictors of subsequent mortality.[44] Together, these data suggest the need for strategies to be developed that improve physiologic (especially cardiopulmonary) reserve before surgery (such as prehabilitation), while also addressing the need to identify complications in a timely manner when they occur (*e.g.*, increased use of monitored postoperative care area, virtual high-dependency monitoring, or close follow-up by rapid response teams). Although supported by face validity, prospective evaluation is required to generate evidence-based recommendations.

For the approximately 40% of the frailty–mortality association that does not appear to be complication-mediated, future research is also required. As people with frailty are at greater risk of death at any time (*i.e.*, regardless of having surgery), preoperative care planning and understanding individuals' preferences and goals of care are especially important for patients with frailty. Preoperative frailty assessment should trigger more careful consideration of patient selection, as surgery is a substantial stressor and people with frailty are typically physiologically vulnerable. Preemptive consideration of palliative care could also be considered, although evidence for palliative care in surgical patients is sparse and suffers from multiple methodologic flaws.[45] However, available evidence is generally positive, with studies reporting an association between frailty assessment–triggered palliative care consultations and decreased mortality,[46] improved communication and decision-making, and symptom management.[45] Other areas of focus could include support for transitions out of hospital, which have been identified as an area of focus for medically complex patients like those with frailty.[47,48]

Strengths and Limitations

Our findings must be appraised in keeping with this study's strengths and limitations. First, we prespecified our approaches in a registered protocol and evaluated the generalizability of our findings using temporally and procedurally separated cohorts. Use of NSQIP data allowed us to utilize complication variables that are typically considered the reference standard in surgical data[49]; however, some definitions in NSQIP (*e.g.*, postoperative myocardial infarction) are likely inadequately sensitive to capture all occurrences as many hospitals do not conduct serial troponin testing in all patients. This may also mean that those identified have more severe presentations, which could bias our results from the null. Furthermore, our methods could not fully disentangle the role of overlapping complication types as mediators, although this warrants future research in people with frailty. Use of Bayesian analyses allowed us to quantify the probability that our findings were true, conditional on our data and previous knowledge, an approach that is more intuitive and less prone to issues of multiplicity than more often used frequentist analyses. However, how our data generalize to non-NSQIP hospitals is unknown. Mediation analyses also require strong control for confounding; while we used best practices to control for a robust set of known confounders, there is no guarantee that unmeasured confounders were not present that could attenuate the magnitude of our findings, which must only be interpreted as associations. Furthermore, as some variables contributed to both the Risk Analysis Index–Administrative score and were included in our models as covariates, adjustment for both could have decreased precision in our estimates. We used a linear parameterization of frailty to avoid the assumptions inherent in categorization

of a continuous variable[50–52]; however, this approach carried its own assumptions. *Post hoc*, we did attempt a tensor-spline parameterization of our frailty instrument; however, even after 20,000 iterations, the frailty parameter demonstrated an unacceptable level of autocorrelation and poor mixing of Markov chains, precluding our ability to use this approach for inference. Hospital-level indicators are also lacking from the NSQIP participant use file data, which precluded us from accounting for the nesting of patients in individual hospitals. Finally, the cause of death for people who did not experience a complication could not be ascertained.

Conclusions

The occurrence of postoperative complications may mediate over half of the observed association between preoperative frailty and postoperative mortality. Future research is needed to develop and evaluate interventions to reduce the incidence of complications and address their impacts in a timely manner. A more in-depth understanding of the direct pathway between frailty and mortality is also required to address non–complication-mediated mortality.

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Competing Interests

The authors declare no competing interests.

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Magneto-Electric Machine's Shocking Treatment: Sparks of Genius or Flash in the Pan?

Energized by electricity's potential, Italian physiologists Luigi Galvani and Alessandro Volta sparked a new scientific field, bioelectromagnetics, in the late eighteenth century. When French neurologist Guillaume Duchenne applied these principles to electrotherapy, American inventor Ari Davis followed with his Davis & Kidder Patent Magneto-Electric Machine (1854, *right*). This portable apparatus could switch between alternating and direct currents. Patients held metal electrodes connected to the Magneto, while an operator turned the crank (*illustrations on left*). Covered in red velvet, the machine's wire-coiled armatures spun past a large blue horseshoe magnet that converted kinetic to electrical energy. The Magneto-Electric Machine delivered around 300 volts—far less than the magnetos of vehicle engines, but more than the transcutaneous electrical nerve stimulation (TENS) units that it prefigured. The device falsely claimed to cure diabetes, neuralgias, and gangrene. After a flash of popularity, it was short-circuited to the quackery pile. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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