ANESTHESIOLOGY

Risk Factors for Failure to Rescue in Myocardial Infarction after Noncardiac Surgery

A Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Patients experiencing perioperative myocardial infarction are at high risk for mortality
- Which patients are at highest risk of failure to rescue (death after a complication)

What This Article Tells Us That Is New

- In a multinational cohort of 8,923 patients experiencing perioperative myocardial infarction after intermediate to high-risk noncardiac surgery, one in five died within 30 days
- Patients age 85 yr or older, and those with advanced systemic disease, underweight body mass index, ascites, disseminated cancer, sepsis, or dyspnea at rest were at highest risk

ABSTRACT

Background: Compared to other perioperative complications, failure to rescue (*i.e.*, death after suffering a complication) is highest after perioperative myocardial infarction (a myocardial infarction that occurs intraoperatively or within 30 days after surgery). The purpose of this study was to identify patient and surgical risk factors for failure to rescue in patients who have had a perioperative myocardial infarction.

Methods: Individuals who experienced a perioperative myocardial infarction after noncardiac surgery between 2012 and 2016 were identified from the American College of Surgeons (Chicago, Illinois) National Surgical Quality Improvement Program database. Multivariable logistic regression was used to identify risk factors for failure to rescue. Subgroup and sensitivity analyses evaluated the robustness of primary findings.

Results: The authors identified 1,307,884 individuals who had intermediate to high-risk noncardiac surgery. A total of 8,923 (0.68%) individuals had a perioperative myocardial infarction, of which 1,726 (19.3%) experienced failure to rescue. Strongest associations (adjusted odds ratio greater than 1.5) were age 85 yr or older (2.52 [95% CI, 2.05 to 3.09] *vs.* age younger than 65 yr), underweight body mass index (1.53 [95% CI, 1.17 to 2.01] *vs.* normal body mass index), American Society of Anesthesiologists class IV (1.76 [95% CI, 1.33 to 2.31] *vs.* class I or II) and class V (3.48 [95% CI, 2.20 to 5.48] *vs.* class I or II), and presence of: ascites (1.81 [95% CI, 1.15 to 2.87]), disseminated cancer (1.54 [95% CI, 1.18 to 2.00]), systemic inflammatory response syndrome (1.55 [95% CI, 1.26 to 1.90]), sepsis (1.75 [95% CI, 1.39 to 2.20]), septic shock (1.79 [95% CI, 1.34 to 2.37]), and dyspnea at rest (1.94 [95% CI, 1.32 to 2.86]). Patients who had emergency surgery, high-risk procedures, and postoperative complications were at higher risk of failure to rescue.

Conclusions: Routinely identified patient and surgical factors predict risk of failure to rescue after perioperative myocardial infarction.

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Major complications after noncardiac surgery are associated with increased mortality, longer hospital stay, and increased medical expenses.[1–6] Perioperative myocardial infarction is a common and serious perioperative complication[7] and it is estimated to occur in approximately 2% of all noncardiac surgeries.[8]

Many deaths after surgery can be attributed to failure to rescue, which is defined as death after suffering a postoperative complication.[9] Failure to rescue is highest after cardiac complications (46% after perioperative myocardial infarction and cardiac arrest[10]), however, it is currently unclear which patients that experience perioperative myocardial infarction are at greatest risk of failure to rescue. This knowledge gap is of particular significance since failure to rescue after perioperative myocardial infarction remains uniformly high between different hospitals, unlike failure to rescue after hemorrhage, sepsis, renal failure, or pneumonia, in which higher performing hospitals having significantly fewer deaths.[11] In addition, recent guideline changes advocating routine perioperative surveillance of troponins will uncover more patients who have experienced a perioperative myocardial infarction.[12]

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This highlights a clear need for strategies to identify individuals at increased risk so that interventions and processes of care can be developed to improve outcomes.

The underlying risk factors that predict failure to rescue after perioperative myocardial infarction have not been identified. Therefore, our primary objective was to identify preoperative, intraoperative, and postoperative risk factors for failure to rescue in individuals that experienced perioperative myocardial infarction after intermediate- to high-risk noncardiac surgery. Our secondary objectives were to determine if these risk factors varied by urgency status and by the underlying cardiac risk of each surgical procedure.

Materials and Methods

This study was registered on Open Science Framework (osf.io/c9u26). The study start date represents the date where the definition of perioperative myocardial infarction was revised to include changes in troponin levels, and 2016 was the last year for which all data sets were complete. Our study is reported according to recommended checklists, including the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[13] and Reporting of studies Conducted using Observational Routinely-collected Data (RECORD)[14] statements (Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/C354). Ethics approval was provided by the Ottawa Health Sciences Research Ethics Board (20160439-01H) and two authors (S.M., D.I.M.) had full access to the data.

Design, Setting, and Data Sources

We performed a retrospective cohort study using patient-level data from all hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program from 2012 to 2016 inclusive. Data were obtained from the American College of Surgeons National Surgical Quality Improvement Program Participant Use File.

The American College of Surgeons National Surgical Quality Improvement Program is a prospective, internally validated registry that records 30-day risk-adjusted surgical outcomes from voluntarily participating hospitals. Data is collected using standard processes employed by trained clinical abstractors. The American College of Surgeons National Surgical Quality Improvement Program database collects perioperative myocardial infarction as a standard and temporally defined outcome. The American College of Surgeons National Surgical Quality Improvement Program Participant Use File database contains deidentified patient information but does not include hospital identifiers, hospital characteristics or patient level clustering. Details of methods of measurement are available in the American College of Surgeons National Surgical Quality Improvement Program Participant Use File guide provided for each year.[15–19]

Participants

We identified all individuals who underwent intermediate- to high-risk noncardiac surgery. Noncardiac surgery was defined as surgery not involving cardiopulmonary bypass or surgical manipulation of the heart. As perioperative myocardial infarction is rare after low-risk surgery and clinical risk stratification is not performed on patients undergoing these procedures,[7] we excluded individuals undergoing low-risk surgery. Procedural risk stratification was performed using Current Procedural Terminology codes as defined recently by Liu *et al.* (Supplemental Digital Content 2, table 2, http://links.lww.com/ALN/C355).[20] We identified individuals with perioperative myocardial infarction based on the American College of Surgeons National Surgical Quality Improvement Program definition during the study period (a perioperative myocardial infarction occurring intraoperatively or within 30 days after surgery as manifested by at least one of two criteria: (1) documentation of electrocardiogram changes indicative of acute myocardial infarction including (one or more of the following): ST elevation greater than 1 mm in two or more contiguous leads, new left bundle branch, and/or new Q-wave in two of more contiguous leads; or (2) new elevation in troponin greater than three times the upper level of the reference range in the setting of suspected myocardial ischemia.[15–17] All individuals classified with a perioperative myocardial infarction formed our study cohort. The primary outcome was failure to rescue, defined as an in-hospital death within the first 30 days after surgery.

Risk Factors for Failure to Rescue

Variables were prespecified based on clinical and epidemiologic knowledge of perioperative myocardial infarction and failure to rescue, as well as from validated American College of Surgeons National Surgical Quality Improvement Program risk calculators[21,22] and the Revised Cardiac Risk Index[23] (variables and definitions are provided in Supplemental Digital Content 3, table 3, http://links.lww.com/ALN/C356). Preoperative variables identified for our study were those that were consistently available and defined in the American College of Surgeons National Surgical Quality Improvement Program Participant Use File for the duration of our study (history of angina, history of cerebrovascular accident/stroke with neurologic deficit, and do not resuscitate status were variables which were considered relevant, but could not be included as they were not available during the duration of the study period). Definitions for disseminated cancer, diabetes mellitus, renal failure, history of chronic obstructive pulmonary disease (COPD), congestive heart failure within 30 days before surgery, hypertension requiring medication, and systemic sepsis did undergo minor changes, but were included in the analysis as these changes were unlikely to materially alter prospective data collection. A postoperative complication included any one of the following: acute renal failure, bleeding transfusion, deep venous

thrombosis/thrombophlebitis, sepsis, septic shock, pneumonia, ventilation, pulmonary embolism, cerebrovascular accident/stroke with neurologic deficit, wound disruption, deep incisional surgical site infection, organ space surgical site infection, first unplanned reoperation, and second unplanned reoperation. Because our research question focused on risk factors for failure to rescue after perioperative myocardial infarction, complications were counted only if they occurred before the perioperative myocardial infarction diagnosis which is time-stamped in American College of Surgeons National Surgical Quality Improvement Program.

Statistical Analysis

All analyses were performed using SAS 9.4 (SAS Institute, USA). Descriptive analyses were undertaken to compare demographics between those who did not experience failure to rescue and those who had. Data that was labeled as "Unknown," "−99," "Null," or "None Assigned" were considered and coded as missing. Descriptive statistics were used to compare characteristics between those who did and did not die after their perioperative myocardial infarction. Continuous variables that were not normally distributed were summarized using median and interquartile range; categorical variables were summarized by frequency and percentage. Wilcoxon rank sum tests were used to compare differences in means for the continuous variables that were not normally distributed; chi-square tests were used to compare differences in proportions for categorical variables. Statistical significance was defined as a two-sided P value less than 0.05.

Primary Analysis. Bivariable logistic regression analysis was used to measure the unadjusted associations between each prespecified predictor and failure to rescue. Our multivariable logistic regression model included all preidentified variables (as opposed to using a variable screening or automated selection process) to calculate the adjusted associations of risk factors with failure to rescue for the following reasons: risk factors for death and for perioperative myocardial infarction are well described in the literature; variable selection algorithms can introduce bias; and important risk factors that lack unadjusted associations can still be significant risk factors in multivariable models.[24–28] A complete case analysis was performed as the primary approach.

Post hoc, to improve the clinical applicability of our findings, we calculated adjusted likelihood ratios from the adjusted odds ratios using the methods of Simel[29] for all predictors with an odds ratio greater than 1.5 (*i.e.,* a moderate effect size or larger). We then combined the likelihood ratios with the prevalence of each predictor to generate posttest probabilities and highlighted predictors where, when present, the posttest probability of mortality after perioperative myocardial infarction would exceed 50%.

Missing Data. Although our multivariable model contained variables likely associated with the probability of data being missing,[30] our complete case analysis could still be biased. Therefore, we performed a sensitivity analysis using multiple imputation to assess the impact of missing data. Continuous variables were imputed using fully conditional regression imputation, while categorical variables were imputed using fully conditional logistic methods. A total of five imputed datasets were created using all prespecified variables using PROC MI (SAS Institute); PROC MIANALYZE (SAS Institute) was used to determine imputation adjusted effect estimates.

Subgroup and Sensitivity Analyses. Subgroup analyses were performed as separate analyses in patients with failure to rescue: (1) for surgical urgency (elective *vs.* emergent surgery), as complication rates and risk of major adverse cardiac events[7,31] vary by surgical urgency; and (2) for procedural cardiac risk (intermediate *vs.* high risk).[20,31] As a sensitivity analysis, we reran our primary analysis but replaced the binary indicator variable for any complication having occurred before the perioperative myocardial infarction with three binary variables indicating predefined high-priority clusters of complications (acute renal failure, sepsis, and respiratory complications [pneumonia or prolonged ventilation]). Our prespecified approach was to first assess for multicollinearity between these variables, and then, if none were present (based on variance inflation factor less than 10), we would include all three together in the primary model, whereas if multicollinearity was present, we would run three separate versions of the primary model, each containing a separate complication cluster. *Post hoc,* we performed a reviewer-requested sensitivity analysis where the binary indicator of intermediate *versus* high cardiac risk was replaced with a three-knot restricted cubic spline of the relative value units for each procedure (a continuous measure of procedural complexity) to assess whether a different and potentially more granular approach to procedural adjustment would substantially change our findings.

Results

Study Population

During the study period, 1,307,884 patients underwent intermediate- and high-risk noncardiac surgery. Of these, 8,923 patients (0.68%) had a perioperative myocardial infarction (fig. 1). Of the patients that had a perioperative myocardial infarction, 1,726 patients (19.3%) experienced failure to rescue. Most baseline characteristics differed significantly between those who experienced failure to rescue and those who did not (table 1). Patients that experienced failure to rescue after perioperative myocardial infarction were older, had higher American Society of Anesthesiologists (ASA) Physical Status classification, and were more likely to have had emergency surgery.

Unadjusted Analysis

There were statistically significant associations between preoperative variables and failure to rescue (table 2). The strongest unadjusted associations (odds ratio greater than 1.5) were age 85 yr or older (2.32 [95% CI, 1.97 to 2.73]),

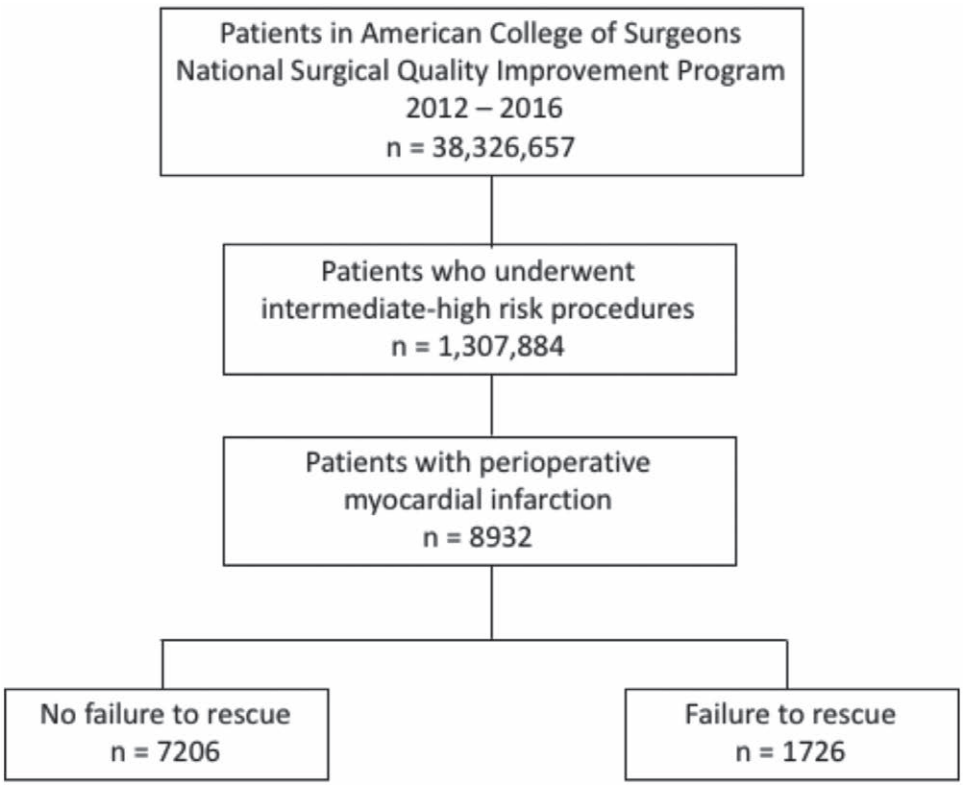

Fig. 1. Consolidated Standards of Report Trials diagram showing schema of study participant selection.

underweight body mass index *versus* normal body mass index (1.69 [95% CI, 1.32 to 2.17]), ASA class III (1.77 [95% CI, 1.40 to 2.23]), ASA class IV (3.00 [95% CI, 2.37 to 3.81]), ASA class V (7.85 [95% CI, 5.36 to 11.5]), ascites (3.09 [95% CI, 2.05 to 4.65]), congestive heart failure within 30 days before surgery (1.93 [95% CI, 1.58 to 2.35]), renal failure (1.72 [95% CI, 1.53 to 1.93]), systemic inflammatory response syndrome (2.12 [95% CI, 1.78 to 2.54]), sepsis (2.49 [95% CI, 2.05 to 3.02]), septic shock (3.29 [95% CI, 2.80 to 3.36]), dyspnea at rest (2.64 [95% CI, 1.88 to 3.71]), transfusion (1.84 [95% CI, 1.48 to 2.29]), emergency surgery (2.51 [95% CI, 2.25 to 2.81]), high-risk surgical procedures (2.15 [95% CI, 1.74 to 2.67]), and any prespecified complication (1.63 [95% CI, 1.44 to 1.84]). Overweight body mass index *versus* normal body mass index (0.70 [95% CI, 0.61 to 0.80]), obese I *versus* normal body mass index (0.68 [95% CI, 0.58 to 0.80]), obese II *versus* normal body mass index (0.66 [95% CI, 0.53 to 0.83]), non–insulin-dependent diabetes mellitus (0.74 [95% CI, 0.64 to 0.87]), and insulin-dependent diabetes mellitus (0.82 [95% CI, 0.71 to 0.94]) were associated with decreased odds of experiencing failure to rescue.

Multivariable Analysis

Multivariable adjusted risk factors and their effect sizes are presented in table 2. After adjustment, anemia (adjusted odds ratio, 0.97 [95% CI, 0.84 to 1.12]) and transfusion (adjusted odds ratio, 1.09 [95% CI, 0.84 to 1.39]) were no longer significantly associated with failure to rescue. Effect size estimates for ASA class III (adjusted odds ratio, 1.48 [95% CI, 1.14 to 1.92]), congestive heart failure (adjusted odds ratio, 1.32 [95% CI, 1.05 to 1.66]), renal failure (adjusted odds ratio, 1.35 [95% CI, 1.16 to 1.58]), emergent surgery (adjusted odds ratio, 1.44 [95% CI, 1.24 to 1.67]), and high-risk surgical procedures (adjusted odds ratio, 1.47 [95% CI, 1.15 to 1.88]) were attenuated after multivariable adjustment. The effect estimate for disseminated cancer was increased after adjustment (adjusted odds ratio, 1.54 [95% CI, 1.18 to 2.00]). The protective effects observed in the unadjusted analysis for obese I *versus* normal body mass index (adjusted odds ratio, 0.93 [95% CI, 0.77 to 1.12]), obese II *versus* normal body mass index (adjusted odds ratio, 0.98 [95% CI, 0.76 to 1.26]), non–insulin-dependent diabetes mellitus (adjusted odds ratio, 0.86 [95% CI, 0.72 to 1.03]), and insulin-dependent diabetes mellitus (adjusted odds ratio, 0.85 [95% CI, 0.72 to 1.01]) were no longer associated with failure to rescue. Additionally, hypertension requiring medication was associated with decreased odds of failure to rescue (adjusted odds ratio, 0.83 [95% CI, 0.71 to 0.97]). The c-statistic for our model was 0.70 indicating an acceptable level of discrimination.[32] The

Table 1. Patient Demographics

Variables	No Failure to Rescue (n = 7,206)	Failure to Rescue (n = 1,726)	*P* Value
Preoperative			
Age, yr			< 0.001
< 65	1,602 (22.2)	287 (16.6)	
65–74	2,169 (30.1)	404 (23.4)	
75–84	2,221 (30.8)	530 (30.7)	
≥ 85	1,214 (16.9)	505 (29.3)	
Male sex	4,017 (55.8)	944 (54.7)	0.434
Surgical specialty			< 0.001
General	2,944 (40.9)	846 (49.0)	
Gynecology	40 (0.56)	5 (0.29)	
Neurosurgery	244 (3.39)	37 (2.14)	
Orthopedics	1,463 (20.3)	405 (23.5)	
Otolaryngology	20 (0.28)	3 (0.17)	
Plastics	20 (0.28)	4 (0.23)	
Thoracic	89 (1.24)	19 (1.10)	
Urology	318 (4.41)	32 (1.85)	
Vascular	2,064 (28.7)	373 (21.6)	
Interventional radiology	4 (0.06)	2 (0.12)	
Body mass index, kg/m^2			< 0.001
Normal (18.50–24.99)	2,117 (31.2)	596 (37.7)	
Underweight (< 18.50)	223 (3.28)	106 (6.70)	
Overweight (≥ 25.00)	2,285 (33.6)	451 (28.5)	
Obese I (30.00–35.00)	1273 (18.7)	243 (15.4)	
Obese II (35.00–40.00)	566 (8.33)	105 (6.64)	
Obese III (≥ 40)	333 (4.90)	81 (5.12)	
ASA classification			< 0.001
I or II	774 (10.8)	88 (5.11)	
III	4,294 (59.7)	864 (50.2)	
IV	2,038 (28.3)	696 (40.4)	
V	84 (1.17)	75 (4.35)	
Ascites	55 (0.76)	40 (2.32)	< 0.001
Disseminated cancer	294 (4.08)	95 (5.50)	0.012
Congestive heart failure	349 (4.84)	154 (8.92)	< 0.001
Diabetes mellitus			< 0.001
None	4,657 (64.6)	1209 (70.1)	
Noninsulin	1,190 (16.5)	229 (13.3)	
Insulin	1,359 (18.9)	288 (16.7)	
Renal failure	1,513 (21.6)	546 (32.1)	< 0.001
Dialysis	386 (5.36)	135 (7.82)	< 0.001
History of severe COPD	942 (13.1)	316 (18.3)	< 0.001
Sepsis			< 0.001
None	6,188 (85.9)	1220 (70.7)	
Systemic inflammatory response syndrome	468 (6.49)	196 (11.6)	
Sepsis	345 (4.79)	169 (9.79)	
Septic Shock	205 (2.84)	141 (8.17)	
Hypertension requiring medication	5,811 (80.6)	1,360 (78.8)	0.086
Steroid use for chronic condition	460 (6.38)	121 (7.01)	0.356
Dyspnea			< 0.001
None	6,157 (85.4)	1,426 (82.62)	
Moderate exertion	959 (13.3)	245 (14.19)	
At rest	90 (1.25)	55 (3.19)	
Anemia	4,497 (67.8)	1,204 (73.73)	< 0.001
Transfusion	291 (4.04)	124 (7.18)	< 0.001
Surgical urgency			< 0.001
Elective	3,955 (55.0)	564 (32.7)	
Emergent	3,241 (45.0)	1,161 (67.3)	
Procedural risk			< 0.001
Intermediate risk	843 (11.7)	100 (5.79)	
High risk	6,363 (88.3)	1,626 (94.2)	
Intraoperative			
Operation time (min) median (interquartile range)	130.0 (77.0–219.0)	111.5 (64.0–188.0)	< 0.001
Postoperative			
Any complication*	1,333 (18.5)	465 (26.9)	< 0.001

Values are n (%) unless otherwise indicated.

*Includes: acute renal failure, bleeding transfusion, deep venous thrombosis/thrombophlebitis, sepsis, septic shock, pneumonia, ventilation, pulmonary embolism, cerebrovascular accident/stroke with neurologic deficit, wound disruption, deep incisional surgical site infection, organ space surgical site infection, unplanned reoperation 1, and unplanned reoperation 2.

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

Table 2. Bivariable and Multivariable Analyses

	Unadjusted Analysis		Adjusted Analysis	
Variables	**Odds Ratio (95% CI)**	***P* Value**	**Odds Ratio (95% CI)**	***P* Value**
Preoperative				
Age, yr				
< 65	Reference group		Reference group	
65–74	1.04 (0.88, 1.23)	0.643	1.18 (0.98, 1.42)	0.076
75–84	1.33 (1.14, 1.56)	< 0.001	1.50 (1.25, 1.80)	< 0.001
≥ 85	2.32 (1.97, 2.73)	< 0.001	2.52 (2.05, 3.09)	< 0.001
Male sex	0.96 (0.86, 1.07)	0.4288	1.09 (0.96, 1.24)	0.168
Body mass index, kg/m^2				
Normal (18.50–24.99)	Reference group		Reference group	
Underweight (< 18.50)	1.69 (1.32, 2.17)	< 0.001	1.53 (1.17, 2.01)	0.002
Overweight (≥ 25.00)	0.70 (0.61, 0.80)	< 0.001	0.83 (0.71, 0.96)	0.013
Obese I (30.00–35.00)	0.68 (0.58, 0.80)	< 0.001	0.93 (0.77, 1.12)	0.426
Obese II (35.00–40.00)	0.66 (0.53, 0.83)	< 0.001	0.98 (0.76, 1.26)	0.843
Obese III (≥ 40)	0.86 (0.67, 1.12)	0.269	1.13 (0.84, 1.52)	0.409
ASA classification				
I or II	Reference group		Reference group	
III	1.77 (1.40, 2.23)	< 0.001	1.48 (1.14, 1.92)	0.003
IV	3.00 (2.37, 3.81)	< 0.001	1.76 (1.33, 2.31)	< 0.001
V	7.85 (5.36, 11.5)	< 0.001	3.48 (2.20, 5.48)	< 0.001
Ascites	3.09 (2.05, 4.65)	< 0.001	1.81 (1.15, 2.87)	0.011
Disseminated cancer	1.37 (1.08, 1.74)	0.009	1.54 (1.18, 2.00)	0.002
Congestive heart failure	1.93 (1.58, 2.35)	< 0.001	1.32 (1.05, 1.66)	0.018
Diabetes mellitus				
None	Reference group		Reference group	
Noninsulin	0.74 (0.64, 0.87)	< 0.001	0.86 (0.72, 1.03)	0.096
Insulin	0.82 (0.71, 0.94)	0.005	0.85 (0.72, 1.01)	0.060
Renal failure	1.72 (1.53, 1.93)	< 0.001	1.35 (1.16, 1.58)	< 0.001
Dialysis	1.50 (1.22, 1.83)	< 0.001	1.13 (0.88, 1.46)	0.352
History of severe COPD	1.49 (1.30, 1.72)	< 0.001	1.34 (1.13, 1.58)	0.001
Systemic sepsis				
None	Reference group		Reference group	
Systemic inflammatory response syndrome	2.12 (1.78, 2.54)	< 0.001	1.55 (1.26, 1.90)	< 0.001
Sepsis	2.49 (2.05, 3.02)	< 0.001	1.75 (1.39, 2.20)	< 0.001
Septic shock	3.49 (2.80, 3.36)	< 0.001	1.79 (1.34, 2.37)	< 0.001
Hypertension requiring medication	0.89 (0.78, 1.02)	0.083	0.83 (0.71, 0.97)	0.022
Steroid use for chronic condition	1.11 (0.90, 1.36)	0.343	1.00 (0.79, 1.26)	0.971
Dyspnea				
None	Reference group		Reference group	
Moderate exertion	1.10 (0.95, 1.28)	0.205	1.05 (0.87, 1.25)	0.628
At rest	2.64 (1.88, 3.71)	< 0.001	1.94 (1.32, 2.86)	0.001
Anemia	1.33 (1.18, 1.51)	< 0.001	0.97 (0.84, 1.12)	0.659
Transfusion	1.84 (1.48, 2.29)	< 0.001	1.09 (0.84, 1.39)	0.525
Surgical urgency				
Elective	Reference group		Reference group	
Emergent	2.51 (2.25, 2.81)	< 0.001	1.44 (1.24, 1.67)	< 0.001
Procedural risk				
Intermediate risk	Reference group		Reference group	
High risk	2.15 (1.74, 2.67)	< 0.001	1.47 (1.15, 1.88)	0.002
Intraoperative				
Operation time (per 10 min)	0.99 (0.98, 0.99)	< 0.001	1.00 (1.00, 1.00)	0.533
Postoperative				
Any complication*	1.63 (1.44, 1.84)	< 0.001	1.43 (1.25, 1.65)	< 0.001

*Includes: acute renal failure, bleeding transfusion, deep venous thrombosis/thrombophlebitis, sepsis, septic shock, pneumonia, ventilation, pulmonary embolism, cerebrovascular accident/stroke with neurologic deficit, wound disruption, deep incisional surgical site infection, organ space surgical site infection, unplanned reoperation 1, and unplanned reoperation 2.

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

Hosmer–Lemeshow P value was $P = 0.920$, indicating that the model was well-calibrated; this was consistent with the calibration plot (fig. 2). No predictors predicted a greater than 50% probability of failure to rescues after perioperative myocardial infarction (Supplemental Digital Content 4, table 4, http://links.lww.com/ALN/C357).

Missing Data

Six variables had missing data: body mass index (6.19%), ASA classification (0.21%), renal failure (2.58%), anemia (7.47%), surgical urgency (0.12%), and operation time (0.03%). The multiple imputed results were consistent with the primary model (Supplemental Digital Content 5, table 5, http://links.lww.com/ALN/C358).

Subgroup and Sensitivity Analyses

Table 3 provides adjusted odds ratios for the elective and emergency groups, and table 4 provides the same for intermediate- and high-risk procedures groups in patients who experienced failure to rescue. Compared to the primary model, the elective surgery-only model did not feature significant associations (adjusted odds ratio greater than 1.50) between underweight body mass index, ASA classifications III, IV, and V, ascites, congestive heart failure within 30 days before surgery, renal failure, history of severe COPD, and septic shock with failure to rescue. However, in the emergent subgroup each remained predictive (except for congestive heart failure [adjusted odds ratio, 1.27 (95% CI, 0.97 to 1.65)]). Any prespecified complication was only significantly associated with increased odds of failure to rescue in the elective surgery group (adjusted odds ratio, 2.28 [95% CI, 1.82 to 2.85]). Hypertension requiring medication was no longer significantly associated with decreased odds of failure to rescue for the elective (adjusted odds ratio, 0.80 [95% CI, 0967 to 1.16]; c-statistic, 0.649) or emergent (adjusted odds ratio, 0.82 [95% CI, 0.67 to 1.00]; c-statistic, 0.679) subgroups.

In the intermediate-risk procedures subgroup age 75 to 84 yr and age 85 yr or older, underweight body mass index, ASA classifications III, IV, and V, disseminated cancer, congestive heart failure within 30 days before surgery, renal failure, history of severe COPD, systematic inflammatory response syndrome, sepsis, septic shock, dyspnea at rest, and emergent surgery were no longer associated with an increased risk of failure to rescue. These variables did remain significantly associated with failure to rescue in the high-risk procedures group. Overweight body mass index *versus* normal body mass index (adjusted odds ratio, 0.84 [95% CI, 0.72 to 0.98]), insulin-dependent diabetes mellitus (adjusted odds ratio, 0.83 [95% CI, 0.69 to 0.98]), and hypertension requiring medication (adjusted odds ratio, 0.81 [95% CI, 0.69 to 0.95]) were significantly associated with decreased odds of failure to rescue in the high-risk procedures group. Since a parameter could not be estimated due to the limited number of exposed individuals, the ascites variable was removed from the procedural risk subgroup analysis. Observed differences in parameter estimates for differential effect were not tested given that this study was underpowered to evaluate these differences.

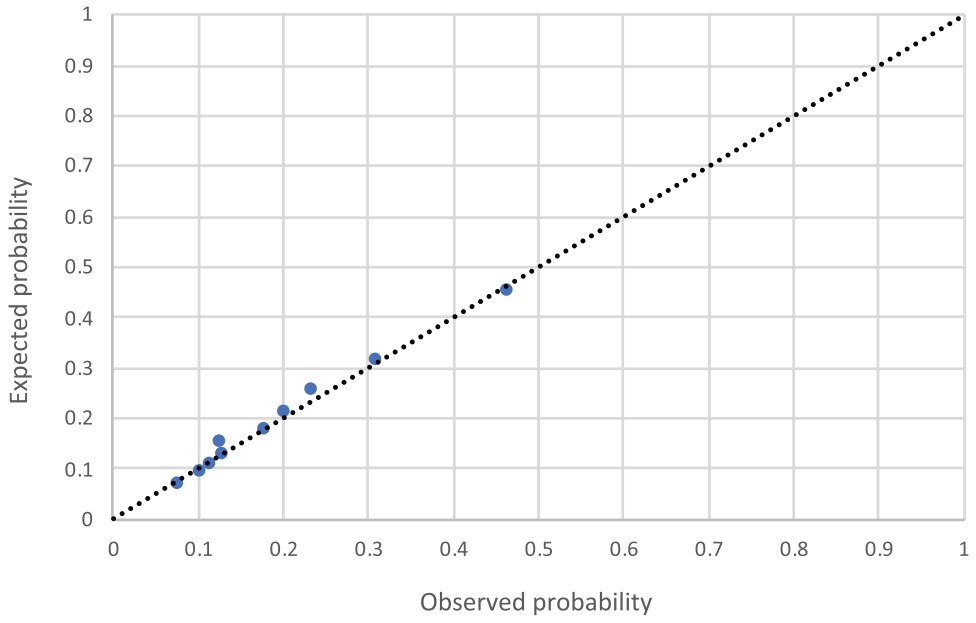

Fig. 2. Calibration plot, Hosmer–Lemeshow plot; $P = 0.920$.

Table 3. Subgroup Analysis of Elective *versus* Emergent Noncardiac Surgery

Variables	Elective Surgery Adjusted Odds Ratio (95% CI)	*P* Value	Emergent Surgery Adjusted Odds Ratio (95% CI)	*P* Value
Preoperative				
Age, yr				
< 65	Reference group		Reference group	
65–74	1.23 (0.93, 1.62)	0.148	1.15 (0.90, 1.48)	0.273
75–84	1.46 (1.10, 1.94)	0.009	1.54 (1.20, 1.96)*	0.001
≥ 85	2.23 (1.56, 3.19)*	< 0.001	2.68 (2.07, 3.47)*	< 0.001
Male sex	1.07 (0.87, 1.31)	0.546	1.15 (0.98, 1.34)	0.091
Body mass index, kg/m^2				
Normal (18.50–24.99)	Reference group		Reference group	
Underweight (< 18.50)	1.23 (0.69, 2.18)	0.484	1.60 (1.17, 2.19)*	0.003
Overweight (≥ 25.00)	0.76 (0.60, 0.98)	0.033	0.87 (0.72, 1.05)	0.143
Obese I (30.00–35.00)	0.99 (0.75, 1.32)	0.966	0.87 (0.68, 1.12)	0.282
Obese II (35.00–40.00)	1.11 (0.77, 1.61)	0.575	0.87 (0.61, 1.24)	0.442
Obese III (≥ 40)	1.29 (0.81, 2.06)	0.291	1.04 (0.71, 1.51)	0.850
ASA classification				
I or II	Reference group		Reference group	
III	1.35 (0.95, 1.91)	0.091	1.63 (1.10, 2.43)*	0.015
IV	1.27 (0.85, 1.89)	0.243	2.18 (1.46, 3.26)*	< 0.001
V	2.40 (0.34, 17.1)	0.383	4.12 (2.39, 7.09)*	< 0.001
Ascites	0.63 (0.07, 5.53)	0.675	1.99 (1.23, 3.22)*	0.005
Disseminated cancer	1.53 (1.03, 2.28)*	0.038	1.57 (1.10, 2.25)*	0.013
Congestive heart failure	1.52 (0.96, 2.41)	0.076	1.27 (0.97, 1.65)	0.083
Diabetes mellitus				
None	Reference group		Reference group	
Noninsulin	0.93 (0.71, 1.21)	0.576	0.81 (0.64, 1.04)	0.095
Insulin	0.83 (0.63, 1.09)	0.177	0.87 (0.70, 1.08)	0.201
Renal failure	1.17 (0.89, 1.55)	0.269	1.44 (1.19, 1.74)	< 0.001
Dialysis	1.31 (0.80, 2.16)	0.288	1.10 (0.81, 1.49)	0.543
History of severe COPD	1.27 (0.97, 1.68)	0.088	1.36 (1.09, 1.68)	0.006
Systemic sepsis				
None	Reference group		Reference group	
Systemic inflammatory response syndrome	2.21 (1.19, 4.11)*	0.012	1.47 (1.18, 1.83)	0.001
Sepsis	3.78 (1.53, 9.35)*	0.004	1.70 (1.34, 2.16)*	< 0.001
Septic shock	0.52 (0.06, 4.87)	0.565	1.72 (1.29, 2.30)*	< 0.001
Hypertension requiring medication	0.80 (0.69, 1.16)	0.404	0.82 (0.67, 1.00)	0.046
Steroid use for chronic condition	0.75 (0.48, 1.18)	0.212	1.11 (0.84, 1.46)	0.480
Dyspnea				
None	Reference group		Reference group	
Moderate exertion	1.15 (0.89, 1.50)	0.292	0.97 (0.75, 1.24)	0.786
At rest	2.79 (1.34, 5.70)*	0.005	1.73 (1.09, 2.75)*	0.019
Anemia	1.08 (0.87, 1.34)	0.500	0.90 (0.74, 1.09)	0.279
Transfusion	1.25 (0.55, 2.87)	0.596	1.09 (0.84, 1.42)	0.516
Procedural risk				
Intermediate risk	Reference group		Reference group	
High risk	1.44 (1.05, 1.98)	0.023	1.54 (1.03, 2.32)*	0.037
Intraoperative				
Operation time (per 10 min)	1.00 (1.00, 1.00)	0.414	1.00 (0.99, 1.01)	0.931
Postoperative				
Any complication†	2.28 (1.82, 2.85)*	< 0.001	1.12 (0.94, 1.33)	0.199

*Adjusted odds ratio of greater than 1.50 was deemed to be clinically significant.

†Includes: acute renal failure, bleeding transfusion, deep venous thrombosis/thrombophlebitis, sepsis, septic shock, pneumonia, ventilation, pulmonary embolism, cerebrovascular accident/stroke with neurologic deficit, wound disruption, deep incisional surgical site infection, organ space surgical site infection, unplanned reoperation 1, and unplanned reoperation 2.

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

In the multivariable model where the binary complication variable was replaced by the three high-priority postoperative complications (acute renal failure, sepsis, and respiratory complications [pneumonia or ventilation]) the variance inflation factor was less than 10 for all variables. Therefore, in the model containing all three complications in addition to pre- and intraoperative factors, we found that acute renal failure (adjusted odds ratio, 1.74 [95% CI, 1.03 to 2.94]) and respiratory complications (adjusted odds ratio, 1.66 [95% CI, 1.35 to 2.04]) were significantly associated

Table 4. Subgroup Analysis of Intermediate- *versus* High-risk Procedures

Variables	Intermediate-risk Procedures Adjusted Odds Ratio (95% CI)	*P* Value	High-risk Procedures Adjusted Odds Ratio (95% CI)	*P* Value
Preoperative				
Age, yr				
< 65	Reference group		Reference group	
65–74	0.73 (0.38, 1.39)	0.332	1.23 (1.01, 1.49)	0.040
75–84	0.64 (0.32, 1.27)	0.200	1.58 (1.31, 1.92)*	< 0.001
≥ 85	1.68 (0.75, 3.76)*	0.204	2.58 (2.09, 3.19)*	< 0.001
Male sex	1.40 (0.82, 2.40)	0.216	1.08 (0.95, 1.23)	0.249
Body mass index, kg/m^2				
Normal (18.50–24.99)	Reference group		Reference group	
Underweight (< 18.50)	4.71 (0.85, 26.2)*	0.077	1.49 (1.13, 1.96)	0.005
Overweight (≥ 25.00)	0.54 (0.28, 1.05)	0.067	0.84 (0.72, 0.98)	0.029
Obese I (30.00–35.00)	0.70 (0.36, 1.39)	0.310	0.94 (0.77, 1.13)	0.496
Obese II (35.00–40.00)	0.59 (0.25, 1.40)	0.228	1.00 (0.77, 1.31)	0.980
Obese III (≥ 40)	0.33 (0.10, 1.06)	0.062	1.26 (0.93, 1.70)	0.142
ASA Classification				
I or II	Reference group		Reference group	
III	1.12 (0.54, 2.32)	0.764	1.56 (1.17, 2.06)*	0.002
IV	1.38 (0.55, 3.49)	0.493	1.84 (1.37, 2.47)*	< 0.001
V	4.51 (0.28, 72.7)*	0.288	3.70 (2.32, 5.93)*	< 0.001
Disseminated cancer	0.51 (0.06, 4.21)	0.528	1.59 (1.22, 2.08)*	0.001
Congestive heart failure	1.20 (0.38, 3.79)	0.752	1.35 (1.07, 1.71)	0.012
Diabetes mellitus				
None	Reference group		Reference group	
Noninsulin	0.83 (0.38, 1.83)	0.647	0.86 (0.71, 1.03)	0.097
Insulin	1.51 (0.79, 2.88)*	0.211	0.83 (0.69, 0.98)	0.033
Renal failure	1.20 (0.58, 2.45)	0.625	1.36 (1.16, 1.59)	< 0.001
Dialysis	1.27 (0.48, 3.32)	0.634	1.13 (0.87, 1.48)	0.356
History of severe COPD	1.76 (0.79, 3.92)*	0.169	1.32 (1.11, 1.57)	0.002
Systemic sepsis				
None	Reference group		Reference group	
Systemic inflammatory response syndrome	0.86 (0.28, 2.71)	0.802	1.59 (1.29, 1.97)*	< 0.001
Sepsis	1.13 (0.37, 3.45)	0.836	1.82 (1.44, 2.30)*	< 0.001
Septic shock	1.56 (0.36, 6.79)*	0.552	1.83 (1.38, 2.43)*	< 0.001
Hypertension requiring medication	1.34 (0.66, 2.73)	0.414	0.81 (0.69, 0.95)	0.010
Steroid use for chronic condition	0.59 (0.21, 1.63)	0.308	1.01 (0.79, 1.29)	0.940
Dyspnea				
None	Reference group		Reference group	
Moderate exertion	0.57 (0.23, 1.43)	0.230	1.08 (0.90, 1.29)	0.430
At rest	1.89 (0.35, 10.1)*	0.458	2.00 (1.34, 2.99)*	0.001
Anemia	1.18 (0.67, 2.11)	0.566	0.97 (0.83, 1.12)	0.662
Transfusion	0.59 (0.12, 3.02)	0.530	1.10 (0.85, 1.41)	0.487
Surgical urgency				
Elective	Reference group		Reference group	< 0.001
Emergent	1.48 (0.78, 2.83)	0.234	1.45 (1.24, 1.69)	
Intraoperative				
Operation time (per 10 min)	1.02 (0.99, 1.05)	0.157	1.00 (1.00, 1.01)	0.745
Postoperative				
Any complication†	2.28 (1.33, 3.92)*	0.003	1.39 (1.21, 1.61)	< 0.001

*Adjusted odds ratio of greater than 1.50 was deemed to be clinically significant. †Includes: acute renal failure, bleeding transfusion, deep venous thrombosis/thrombophlebitis, sepsis, septic shock, pneumonia, ventilation, pulmonary embolism, cerebrovascular accident/stroke with neurologic deficit, wound disruption, deep incisional surgical site infection, organ space surgical site infection, unplanned reoperation 1, and unplanned reoperation 2.

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with failure to rescue after perioperative myocardial infarction, while sepsis was not (Supplemental Digital Content 6, table 6, http://links.lww.com/ALN/C359). There were minimal differences in a *post hoc* sensitivity analysis adjusting for procedural risk (Supplemental Digital Content 7, table 7, http://links.lww.com/ALN/C360).

Discussion

In this cohort study using a representative American and Canadian surgical database, we found that 19% of patients who had a perioperative myocardial infarction experienced failure to rescue. Preoperative risk factors that were strongly associated with failure to rescue after perioperative

myocardial infarction included patient factors (advanced age, low body mass index) and comorbid factors (high ASA class, ascites, disseminated cancer, presence of congestive heart failure, renal failure, systemic inflammatory response syndrome, sepsis, septic shock, dyspnea at rest). Death in a patient who has suffered a complication may represent a missed opportunity to rescue the patient (*i.e.,* processes of care or interventions that may have prevented the death were not engaged). These findings suggest that when caring for patients with these risk factors who experience perioperative myocardial infarction, a high index of suspicion for death is required, as well as consideration of strategies to attenuate risk. These characteristics could also inform patient selection for interventional trials testing therapies to achieve effective rescue when perioperative myocardial infarction does occur.

Our finding that almost one in five individuals who have a perioperative myocardial infarction after surgery die during the first 30 days of their hospitalization is significant for several reasons. First, although our failure to rescue rate after perioperative myocardial infarction is lower than that reported by Ferraris *et al.*[10] (who considered perioperative myocardial infarction, cardiac arrest, or both), by limiting our cohort to perioperative myocardial infarction, our findings may be more clinically relevant as cardiac arrest is a postoperative complication with a high association with death,[33] and one that requires a specific treatment protocol.[34,35] However, our rate of perioperative myocardial infarction is lower than that observed in prospective randomized perioperative trials where approximately 6% of patients experienced myocardial infarction.[36,37] This may be due to the use of the American College of Surgeons National Surgical Quality Improvement Program perioperative myocardial infarction definition, which would capture only perioperative myocardial infarctions that were clinically identified, typically in the absence of universal screening (*vs.* identification through routine screening approaches to case identification used in those trials), and may therefore be of increased severity. Therefore, our lower incidence likely reflects the differential definitions used and represents a known limitation of the National Surgical Quality Improvement Program outcome definitions. Finally, with a rate of 19%, perioperative myocardial infarction has a higher risk of failure to rescue than pulmonary embolism (9%)[38] and approaches that of septic shock (34%).[38] This high rate of failure to rescue suggests that further research is needed to help identify at-risk patients and to develop both therapies and care processes that will reduce failure-to-rescue rates.

While preoperative risk stratification for mortality and cardiac complications is well-established,[21–23,39] our study provides novel insights into the risk of death in those who have already experienced a postoperative cardiac complication. Within this context, it was not surprising that several factors included in the Revised Cardiac Risk Index[23] and the American College of Surgeons National Surgical Quality Improvement Program cardiac risk calculator[22] (procedural risk, renal failure, advanced age, ASA class, and congestive heart failure) were also significant predictors of failure to rescue after perioperative myocardial infarction. Furthermore, age, surgical risk, and ASA class each demonstrated a dose–response relationship, where higher values were associated with greater risk. The Revised Cardiac Risk Index[23] identifies functional status as an independent predictor; although functional status is a historical variable and was not available in American College of Surgeons National Surgical Quality Improvement Program during the study period, we found that dyspnea at rest was strongly associated with failure to rescue and could be a potential surrogate for functional status. We also identified several factors associated with failure to rescue after perioperative myocardial infarction that were not included in existing preoperative risk calculators. These included underweight body mass index and the presence of significant systemic infection, specifically systemic inflammatory response syndrome, sepsis, and septic shock. Importantly, there was a clear increase in risk when sepsis and septic shock were present (compared to systemic inflammatory response syndrome) which may suggest an important interplay between infectious and cardiac complications in perioperative patients. This may warrant investigation in future studies.

Of particular note is failure to rescue in patients who have had a perioperative myocardial infarction after elective surgery. Although emergent surgery is well recognized to have an increased risk of morbidity and mortality, elective surgery does not.[40] Thus, any complications associated with elective surgery may be particularly devastating to patients and their caregivers. Within our study population, the strongest predictors of failure to rescue in patients undergoing elective surgery were age greater than 85 yr old, systemic inflammatory response syndrome, sepsis, dyspnea at rest, disseminated cancer, and the presence of any postoperative complication.

By identifying individuals at high-risk of failure to rescue after perioperative myocardial infarction, allocation of available resources may be improved and appropriate strategies to mitigate the risk of death may be developed. Strategies to consider may include initiation of oral anticoagulants in this high-risk population[41] or the initiation of interdisciplinary postoperative care,[42] both of which have been demonstrated to reduce mortality in other high-risk populations. However, the body of literature describing interventions to improve outcomes after perioperative myocardial infarction is sparse,[12] and we lack data to demonstrate that the associations described represent true causal mechanisms. However, knowledge of which patients are at the greatest risk of failure to rescue after perioperative myocardial infarction could help to inform interventional study designs by enrolling high-risk individuals who may be most likely to benefit from interventions.

Strengths and Limitations

Our protocol was registered *a priori*, therefore variables considered and analyses performed were prespecified. By using data from the American College of Surgeons National Surgical

Quality Improvement Program, we were able to leverage prospectively collected data to define our cohort, exposure, outcome, and predictors, reducing risk of misclassification bias. Since the American College of Surgeons National Surgical Quality Improvement Program data are temporally coded, we could also properly account for other complications on the causal pathway to mortality. The American College of Surgeons National Surgical Quality Improvement Program definition of perioperative myocardial infarction is highly specific, which is a strength in that individuals included in our cohort had a high certainty of having had a perioperative myocardial infarction. However, the definition of myocardial infarction used may miss patients who are asymptomatic. It is unclear what effect these patients with "silent" myocardial infarctions may have had on our results. As a retrospective analysis using observational data, we can report only associations; causality cannot be inferred, nor can cause of death be ascertained. Our findings may apply only to those with clinically diagnosed perioperative myocardial infarction and cannot be directly generalized to those with asymptomatic perioperative myocardial infarctions identified through universal screening. Future research will be required to evaluate whether inclusion of such individuals would change the relative impact of our identified predictors. In addition, deaths that occur after 30 days are not accounted for in this analysis. We were also unable to account for hospital-level predictors, such as volume and baseline mortality rates that may also influence postoperative outcomes, although it has been suggested that postoperative complications are related more to patient factors than to quality of care.[43] Moreover, as detailed in the discussion, failure to rescue after perioperative myocardial infarction was uniformly high among hospitals; this suggests that patient factors may outweigh hospital-level predictors for failure to rescue after perioperative myocardial infarction.[11]

In conclusion, failure to rescue after perioperative myocardial infarction is common after noncardiac surgery and is associated with a number of demographic, clinical, and surgical factors. Our findings will aid future research that may determine how postoperative complications in this high-risk group can be detected early, treated more effectively, or potentially avoided altogether.

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Competing Interests

The authors declare no competing interests.

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