EDITORIAL

Left Ventricular Function as a Predictor of Noncardiac Surgical Procedural Outcome

John S. Ikonomidis, MD, PhD

A new study[1] published in the February 12, 2019, issue of *JAMA* documents the negative association of depressed left ventricular function and associated heart failure symptoms on outcomes with noncardiac surgical procedures. Risk stratification prior to the performance of surgery has become an important aspect of preoperative planning. Robust databases now exist to allow surgeons to calculate surgical risk of mortality and other complications for a wide variety of procedures adjusted for a myriad of comorbidities. In the cardiac surgical realm, an important predictor of adverse outcome is depressed left ventricular function, a factor that is so important it often dominates multivariable regression analyses predictive of mortality and other postoperative complications.

Related article at jama.com

Poor left ventricular function has also long been known to be a predictor of adverse outcome in noncardiac surgery, but this knowledge alone is an incomplete assessment. More information is needed regarding the effects of varying degrees of ventricular dysfunction, the presence or absence of heart failure symptoms, different heart failure types (reduced ejection fraction heart failure and normal ejection fraction heart failure), and the influence of procedural complexity.

In this week's issue of *JAMA*, Lerman and colleagues[1] determined the postoperative mortality risk of symptomatic and asymptomatic patients with heart failure, with and without preserved ejection fraction, compared with patients without heart failure. The data set was assembled from 609 735 noncardiac surgical patient records in the Veterans Affairs Surgical Quality Improvement Project database from 2009 to 2017. Left ventricular ejection fraction estimates were taken from associated echocardiogram reports, heart failure was documented by frequency of hospital admissions with a heart failure diagnosis and the presence of heart failure symptoms, and 3 levels of surgical procedural complexity were defined using the VA Surgical Complexity Matrix. Three multivariable mixed-effects logistic regression models were generated, the first comparing the postoperative mortality risk of all patients with and without heart failure, the second classifying patients with heart failure by left ventricular ejection fraction stratified into 4 levels, and the third model classifying patients with heart failure by the presence of heart failure symptoms.

The results of the analysis revealed that, compared with patients without heart failure, patients with heart failure experienced higher risk of 90-day postoperative mortality (mortality risk: 5.49% vs 1.22%). Compared with patients without heart failure, symptomatic patients with heart failure experienced greater risk (odds ratio, 2.37), and asymptomatic patients with heart failure (odds ratio, 1.53) including those patients with preserved left ventricular systolic function (odds ratio, 1.46) also experienced elevated risk. The crude 90-day postoperative mortality for patients with heart failure increased from 4.6% for standard complexity operations to 10.3% for complex procedures, and the postoperative mortality was 0.7% to 6.2% among patients with and without heart failure, respectively. For patients without heart failure, crude 90-day postoperative mortality increased from 0.7% to 6.2% (standard to complex). Overall, the adjusted absolute risk difference between patients with and without heart failure was 1.29% (95% CI, 1.22%-1.37%) for standard procedures, 1.69% (95% CI, 1.48%-1.94%) for intermediate procedures, and 1.80% (95% CI, 0.08-3.60) for complex procedures.

This is a well-written and well-reported study. In contrast to previous studies, this analysis provides a more detailed description of the associations of increasing levels of systolic dysfunction and the presence or absence of heart failure symptoms with surgical outcomes than previously documented. As the authors point out, the data set reflects an inherent selection bias because all patients analyzed were deemed fit for surgery, and hence no inferences can be drawn regarding patients who were considered for but did not receive surgery. In addition, as this is a Veterans Affairs patient population, the data set only comprised 8.6% female patients. However, the absolute number of female patients (52 563, of which 1391 had heart failure) is considerable. Overall, the data reported here is highly valuable and comprehensive information that practitioners can use for preoperative planning and also in discussions with patients.

ARTICLE INFORMATION

Author Affiliation: Division of Cardiothoracic Surgery, University of North Carolina at Chapel Hill, Chapel Hill.

Corresponding Author: John S. Ikonomidis, MD, PhD, Division of Cardiothoracic Surgery, University of North Carolina at Chapel Hill, 3034 Burnett Womack Bldg, 160 Dental Circle, Chapel Hill, NC 27599 (john_ikonomidis@med.unc.edu).

Published Online: February 12, 2019. doi:10.1001/jamasurg.2019.0243

Conflict of Interest Disclosures: None reported.

REFERENCE

1. Lerman BJ, Popat RA, Assimes TL, Heidenreich PA, Wren SM. Association of left ventricular ejection fraction and symptoms with mortality after elective noncardiac surgery among patients with heart failure [published online February 12, 2019]. *JAMA*. doi:10.1001/jama.2019.0156

JAMA | Original Investigation

Association of Left Ventricular Ejection Fraction and Symptoms With Mortality After Elective Noncardiac Surgery Among Patients With Heart Failure

Benjamin J. Lerman, BS; Rita A. Popat, PhD; Themistocles L. Assimes, MD, PhD; Paul A. Heidenreich, MD, MS; Sherry M. Wren, MD

Related article page 602

Supplemental content

IMPORTANCE Heart failure is an established risk factor for postoperative mortality, but how left ventricular ejection fraction and heart failure symptoms affect surgical outcomes is not fully described.

OBJECTIVES To determine the risk of postoperative mortality among patients with heart failure at various levels of echocardiographic (left ventricular systolic dysfunction) and clinical (symptoms) severity compared with those without heart failure and to evaluate how risk varies across levels of surgical complexity.

DESIGN, SETTING, AND PARTICIPANTS US multisite retrospective cohort study of all adult patients receiving elective, noncardiac surgery in the Veterans Affairs Surgical Quality Improvement Project database from 2009 through 2016. A total of 609 735 patient records were identified and analyzed with 1 year of follow-up after having surgery (final study follow-up: September 1, 2017).

EXPOSURES Heart failure, left ventricular ejection fraction, and presence of signs or symptoms of heart failure within 30 days of surgery.

MAIN OUTCOME AND MEASURE The primary outcome was postoperative mortality at 90 days.

RESULTS Outcome data from 47 997 patients with heart failure (7.9%; mean [SD] age, 68.6 [10.1] years; 1391 women [2.9%]) and 561 738 patients without heart failure (92.1%; mean [SD] age, 59.4 [13.4] years; 50 862 women [9.1%]) were analyzed. Compared with patients without heart failure, those with heart failure had a higher risk of 90-day postoperative mortality (2635 vs 6881 90-day deaths; crude mortality risk, 5.49% vs 1.22%; adjusted absolute risk difference [RD], 1.03% [95% CI, 0.91%-1.15%]; adjusted odds ratio [OR], 1.67 [95% CI, 1.57-1.76]). Compared with patients without heart failure, symptomatic patients with heart failure (n = 5906) had a higher risk (597 deaths [10.11%]; adjusted absolute RD, 2.37% [95% CI, 2.06%-2.57%]; adjusted OR, 2.37 [95% CI, 2.14-2.63]). Asymptomatic patients with heart failure (n = 42 091) (2038 deaths [crude risk, 4.84%]; adjusted absolute RD, 0.74% [95% CI, 0.63%-0.87%]; adjusted OR, 1.53 [95% CI, 1.44-1.63]), including the subset with preserved left ventricular systolic function (1144 deaths [4.42%]; adjusted absolute RD, 0.66% [95% CI, 0.54%-0.79%]; adjusted OR, 1.46 [95% CI, 1.35-1.57]), also experienced elevated risk.

CONCLUSIONS AND RELEVANCE Among patients undergoing elective noncardiac surgery, heart failure with or without symptoms was significantly associated with 90-day postoperative mortality. These data may be helpful in preoperative discussions with patients with heart failure undergoing noncardiac surgery.

JAMA. 2019;321(6):572-579. doi:10.1001/jama.2019.0156

Author Affiliations: Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California (Lerman, Popat); Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California (Assimes, Heidenreich); Medical Service, Section of Cardiology, Palo Alto Veterans Affairs Health Care System, Palo Alto, California (Assimes, Heidenreich); Division of General Surgery, Palo Alto Veterans Affairs Health Care System, Palo Alto, California (Wren); Department of Surgery, Stanford University School of Medicine, Stanford, California (Wren).

Corresponding Author: Sherry M. Wren, MD, Department of Surgery, Stanford University, G112 PAVAHCS, 3801 Miranda Ave, Palo Alto, CA 94304 (swren@stanford.edu).

Heart failure results from inadequate cardiac output and can be associated with symptoms of dyspnea, edema, and fatigue. These symptoms may or may not be present and, more recently, attention has been drawn to 2 major subtypes of symptomatic heart failure: reduced ejection fraction heart failure and preserved ejection fraction heart failure. Heart failure has been long recognized as a risk factor for postoperative mortality.[1,2] However, most prior studies examining the relationship between heart failure and postoperative mortality have not accounted for the various subtypes of this disease. Because of heart failure's importance as a risk factor for adverse surgical outcomes, it is common to include heart failure in operative risk prediction models, but most of these models were developed without accounting for the different subtypes of heart failure.[1,3-7]

Both left ventricular ejection fraction (LVEF) and the presence of heart failure symptoms are associated with long-term mortality rates in patients with heart failure, but the degree to which these factors influence postoperative risk is not fully described.[8-10] Previous studies evaluating the association between LVEF or symptoms and postoperative mortality were too small to fully describe the effects of LVEF or had focused on individual subpopulations of patients with heart failure, which limited their generalizability to the overall heart failure population.[11-13] Furthermore, much of the literature relied on a clinical definition of heart failure, which only captured patients with signs or symptoms of heart failure. This excludes assessment of asymptomatic patients who may also have an increased risk of postoperative mortality. The purpose of this study was to determine the postoperative mortality risk of symptomatic and asymptomatic patients with heart failure, with and without preserved ejection fraction, compared with patients without heart failure.

Key Points

Question What is the association between severity of heart failure and risk of postoperative mortality?

Results In this retrospective cohort study that included 609 735 patients undergoing noncardiac surgery, crude 90-day mortality for patients with heart failure and symptoms was 10.1%; for patients with heart failure and no symptoms, 4.9%; and for patients without heart failure, 1.2%. The adjusted differences between either group of patients with heart failure and those without heart failure were statistically significant.

Meaning Heart failure with or without symptoms was associated with increased risk of 90-day postoperative mortality.

Methods

Study Approval, Data Sources, and Study Population

This study was approved by the Stanford University Institutional Review Board (No. 42246) and Department of Veterans Affairs (RDIS No. WRE0013), and a waiver of informed consent was obtained. Two national Veterans Affairs (VA) databases were used to assemble the cohort. One was data obtained by the VA Surgical Quality Improvement Program (VASQIP), which has trained data extractors who sample a fraction of cases at individual facilities and enter detailed clinical information into a centralized database.[14,15] For information not available from VASQIP, the VA Corporate Data Warehouse (CDW) was used, which extracts data directly from the VA electronic medical records system. Medical comorbidities for each participant were extracted from VASQIP (hypertension, stroke, chronic obstructive pulmonary disease, peripheral vascular disease, disseminated cancer) and from CDW diagnostic codes (atrial fibrillation, diabetes mellitus, asthma, aortic stenosis, mitral regurgitation, pulmonary hypertension). Left ventricular ejection fraction was obtained from echocardiogram reports using a previously validated natural language processing algorithm.[16,17] Follow-up data were available for each participant for a minimum of 1 year.

All VASQIP-sampled procedures from fiscal years 2009 through 2016 were eligible for inclusion, with the final date of follow-up September 1, 2017. Cardiac procedures, emergent procedures, and nonsurgical procedures (ie, bronchoscopy, endoscopy) were excluded. All patients undergoing multiple eligible procedures within the study period contributed only their index procedure.

Classification of Heart Failure and Subpopulations

The classification of heart failure by diagnostic codes in the VA health care system is highly specific (>95%) and has good sensitivity (75%-90%).[18-21] Patients were classified as having heart failure if they had at least 1 inpatient admission or at least 2 outpatient clinic visits with a diagnosis of heart failure by an *International Classification of Diseases* (*ICD*) code within 3 years of surgery.[22] These criteria properly excluded patients with a single outpatient visit for whom heart failure was excluded following evaluation. Patients with heart failure were further subdivided by LVEF (if an echocardiogram within 5 years of surgery was available) and presence of heart failure signs and symptoms. The following established cutoffs were used for LVEF: preserved, 50% or more; mildly reduced, 40% through 49%; moderately reduced, 30% through 39%; and severely reduced, less than 30%.[23] Patients were classified as having symptomatic heart failure by the American College of Surgeons-NSQIP definition: newly diagnosed or chronic heart failure with signs or symptoms in the 30 days prior to surgery.[24]

Surgical Complexity

Procedures were classified by the VA Surgical Complexity Matrix, which the VA health care system uses to determine which facilities can safely perform certain surgical procedures.[25,26] This system assigned a complexity level (standard, intermediate, or complex) to every *Current Procedural Terminology* code based on intraoperative and postoperative risk inherent to the procedure (eTable 1 in the Supplement). Surgical complexity was included as a covariate in the final multivariable models.

Outcomes

The primary outcome of this study was all-cause, 90-day, postoperative mortality. Secondary outcomes were 30-day and 1-year postoperative mortality. Post hoc analyses of 30-day postoperative complications (any), 30-day postoperative cardiac arrest, 30-day postoperative myocardial infarction, 30-day postoperative stroke, and a 72-hour postoperative bleeding event (defined as transfusion for any reason of >4 U of packed red blood cells or whole blood after the patient has left the operating room) were also conducted. Date of death was determined via Social Security Administration Death Master Files.

Statistical Methods

Demographic and clinical characteristics of patients with and without heart failure were compared with χ^2 tests for categorical variables and unpaired *t* tests for continuous variables. Odds ratios (ORs) were generated using simple or multivariable logistic regression, and 95% confidence intervals computed with the Wald χ^2. Potential confounders were assessed based on a priori knowledge and the literature.[6,27] The following factors were considered: sex, race/ethnicity, age, body mass index, smoking, alcohol use, hypertension, atrial fibrillation, diabetes mellitus, coronary artery disease, history of stroke, asthma, chronic obstructive pulmonary disease, peripheral vascular disease, disseminated cancer, surgical complexity level, American Society of Anesthesiologists (ASA) class,[28] aortic stenosis, mitral regurgitation, pulmonary hypertension, VA facility, and preoperative creatinine and preoperative hematocrit levels. Covariates were screened by individual addition to the univariable model, and those that altered the exposure estimate by 10% or more were included in the final model.

Race/ethnicity is associated with long-term survival in patients with heart failure and was thus included as a covariate.[29] Race/ethnicity classification was determined by the participant and was based on a fixed-categories questionnaire.

The final analysis consisted of 3 multivariable mixed-effects logistic regression models with random intercepts to account for clustering by VA facility. The models adjusted for all other variables as fixed effects in an identical fashion to a traditional multivariable logistic regression model.[30] Each model used patients without heart failure as the reference group but organized patients with heart failure using a different, preplanned classification scheme. The first model compared the postoperative mortality risk of all patients with and without heart failure. The second model classified patients with heart failure (the primary exposure) by their left ventricular ejection fraction (4 levels). The third model classified patients with heart failure by the presence of heart failure symptoms (2 levels). Propensity score-adjusted models were also built as a sensitivity analysis. Propensity scores for heart failure for each participant were built using the predicted probabilities resulting from a multivariable logistic regression model with heart failure as the outcome and all identified potential confounders identified (as described above) as variables in the model. As a sensitivity analysis to assess the potential influence of unmeasured confounders on the analysis, E-values were calculated.[31] The E-value represents the minimum magnitude of association required between an unmeasured confounder and both the exposure and outcome, conditional on measured covariates, to fully attenuate the observed exposure-outcome relationship.[31] An E-value was calculated for the observed overall heart failure postoperative mortality association using a publicly available online calculator.[32]

Stratified analyses were also conducted by surgical complexity level, and interactions were tested between the primary exposure (heart failure, yes or no) and the level of complexity of the surgery performed (standard, intermediate, or complex). *P* for interaction was calculated using the likelihood ratio test. All ORs and absolute risk differences (RDs) presented are adjusted unless explicitly identified as crude. Average adjusted predicted probabilities for each group were calculated using the above regression models, and adjusted absolute RDs between the exposed and unexposed groups were then calculated. Adjusted attributable risk fraction was calculated by the following formula: (adjusted OR −1)/(adjusted OR). Relevant *P* values for trend were calculated with the Wald χ^2 after converting the categorical LVEF or symptom variables into a continuous variable.

Post hoc analyses of the association between heart failure and postoperative complications were conducted using multivariable logistic regression, and post hoc analysis of the association between heart failure and postoperative length of stay were conducted using multivariable linear regression adjusted for the confounders identified as above.

The proportion of missing nonlaboratory, nonimaging covariates was less than 1%. Missing observations were excluded from the analysis. Missing preoperative laboratory values (missing at 6%-7%) were imputed with a single conditional imputation approach using age- and sex-adjusted norms. Left ventricular ejection fraction, as measured by echocardiogram, was missing in 2.9% of patients with heart failure, and patients with missing LVEF were excluded from subset analyses pertaining to left ventricular systolic function.

Based on the sample size of the cohort included in this analysis (n = 609 735, 7.9% heart failure) this study had 99.9% power to detect ORs of more than 1.5 for the heart failure and postoperative mortality association at $\alpha = .05$.[3,12] SAS version 9.4 (SAS Institute Inc) was used for all analyses. All tests with 2-sided *P* values <.05 were considered statistically significant.

Results

Cohort Characteristics

Of the 609 735 patients in this cohort, 47 997 (7.9%) had a clinical history of heart failure (**Table 1**). Patients with heart failure were more likely to be men (97.1% vs 91.0%), white (67.6% vs 64.5%), obese (44.4% vs 38.7%), and older (69 vs 59 years); had higher rates of medical comorbidities; and had higher ASA scores (mean, 3.3 vs 2.7) than patients without heart failure. At the time of surgery, patients with heart failure had higher creatinine levels (median, 1.10 mg/dL vs 0.97 mg/dL) and lower hematocrit levels (mean, 38.1% vs 41.6%). (To convert creatinine from mg/dL to μmol/L, multiply by 88.4.)

Table 1. Demographics and Medical History of Patients With and Without Heart Failure

	Heart Failure[a]	Without Heart Failure
Total No. (%)	47 997 (7.9)	561 738 (92.1)
Demographics		
Sex, No. (%)		
Women	1391 (2.9)	50 862 (9.1)
Men	46 606 (97.1)	510 876 (91.0)
Race/ethnicity, No. (%)		
White, non-Hispanic	32 421 (67.6)	362 562 (64.5)
Black, non-Hispanic	7821 (16.3)	86 229 (15.4)
Hispanic	1743 (3.6)	26 212 (4.7)
Other	390 (0.8)	6909 (1.2)
Not reported	5622 (11.7)	79 826 (14.2)
Age, mean (SD), y	68.6 (10.1)	59.4 (13.4)
BMI, mean (SD)	29.9 (6.9)	29.0 (5.8)
Current smoker, No. (%)	13 806 (27.3)	182 714 (32.5)
Current alcohol use, No. (%)	2513 (5.2)	41 593 (7.4)
Medical history, No. (%)[b]		
Hypertension	42 077 (87.7)	324 918 (57.9)
Coronary artery disease	32 159 (67.0)	110 251 (19.6)
Diabetes mellitus	28 332 (59.0)	175 640 (31.3)
Atrial fibrillation	18 998 (39.6)	49 145 (8.8)
Chronic obstructive pulmonary disease	13 580 (28.3)	60 710 (10.8)
History of stroke	6214 (13.0)	25 262 (4.5)
Peripheral vascular disease	5611 (11.7)	16 591 (3.0)
Asthma	4371 (9.1)	43 710 (7.8)
Aortic stenosis	3549 (7.4)	10 578 (1.9)
Mitral regurgitation	2340 (4.9)	5687 (1.0)
Pulmonary hypertension	1934 (4.0)	2991 (0.5)
Disseminated cancer	689 (1.4)	5430 (1.0)
American Society of Anesthesiologists class, No. (%)[c]		
I (Healthiest)	27 (0.1)	17 074 (3.0)
II	1449 (3.0)	176 783 (31.5)
III	31 255 (65.1)	337 757 (60.1)
IV	15 153 (31.6)	29 965 (5.3)
V (Sickest)	113 (0.2)	159 (<0.1)
Preoperative laboratory values[d]		
Creatinine, median (IQR), mg/dL	1.10 (0.90-1.48)	0.97 (0.82-1.10)
Hematocrit, mean (SD), %	38.1 (6.1)	41.6 (4.8)
Surgical complexity, No. (%)[e]		
Standard	25 327 (52.8)	341 749 (60.8)
Intermediate	21 509 (44.8)	209 022 (37.2)
Complex	1161 (2.4)	10 967 (2.0)
Surgical disposition[f]		
Ambulatory	19 551 (40.7)	337 150 (60.0)
Inpatient	28 445 (59.3)	224 575 (40.0)
Anesthesia technique, No. (%)[g]		
General	38 606 (80.5)	488 837 (87.0)
Epidural/spinal	3730 (7.8)	30 078 (5.4)
Monitored anesthesia care	3919 (8.2)	28 348 (5.1)
Local	3764 (0.7)	477 (1.0)
Other	1258 (2.6)	10 622 (1.9)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range.

SI conversion factor: to convert creatinine from mg/dL to μmol/L, multiply by 88.4.

[a] *P* < .001 for all comparisons. Nonnormal distributions presented as median (IQR); normally distributed continuous variables, mean (SD).

[b] Medical comorbidities were derived from chart extraction by trained Veterans Affairs Surgical Quality Improvement Program nurses (hypertension, stroke, chronic obstructive pulmonary disease, peripheral vascular disease, disseminated cancer) and by the *International Statistical Classifications of Diseases* diagnostic codes in the electronic medical record (atrial fibrillation, diabetes mellitus, asthma, aortic stenosis, mitral regurgitation, pulmonary hypertension).

[c] The American Society of Anesthesiologists Physical Status Classification is a subjective assessment of a patient's overall health by a physician. The classification ranges from I (a normal healthy patient) to V (a moribund patient who is not expected to survive without the operation).

[d] Creatinine measures are missing for 6.9%; hematocrit, 7.3%.

[e] Surgical complexity reflects assignment in the VA Surgical Complexity matrix, which assigns every surgical procedure (by *Current Procedural Code* code) a value of standard, intermediate, or complex by its intraoperative and perioperative risk to the patient.

[f] *Inpatient* is defined as a surgery after which the patient stays at least 1 night as an inpatient in the hospital. *Ambulatory* is defined as a surgery after which the patient is discharged home without staying overnight in the hospital. Does not include 14 patients with missing disposition.

[g] Does not include 96 patients with missing anesthesia technique.

Left ventricular ejection fraction data were available for 97.1% of patients with heart failure (eTable 2 in the Supplement). A total of 28 742 patients (59.9%) had documented preserved systolic function (LVEF, ≥50%). Of these, 2851 (9.9%) had symptoms and 25 891 (90.1%) did not. A total of 7612 patients (15.9%) had mildly reduced systolic function (LVEF, 40%-49%; 1033 [13.6%] with symptoms, 6579 [86.4%] without symptoms), 6048 patients (12.6%) had moderately

Table 2. Adjusted Odds Ratios and Risk Differences of 90-Day Postoperative Mortality Between Patients With and Without Heart Failure

	No. of Patients	Crude Mortality (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	Crude Absolute Risk Difference (95% CI), %	Adjusted Absolute Risk Difference (95% CI), %[b]
Model 1: heart failure (overall)						
Without heart failure	561 738	1.22	1 [Reference]	1 [Reference]	Reference	Reference
Heart failure	47 997	5.49	4.68 (4.47-4.90)	1.67 (1.57-1.76)	4.26 (4.15-4.38)	1.03 (0.91-1.15)
Model 2: heart failure defined by systolic function[c]						
Without heart failure	561 738	1.22	1 [Reference]	1 [Reference]	Reference	Reference
Heart failure						
Preserved LVEF (≥50%)	28 742	4.88	4.14 (3.90-4.39)	1.51 (1.40-1.62)	3.66 (3.52-3.80)	0.72 (0.61-0.84)
Mildly reduced LVEF (40%-49%)	7612	5.11	4.34 (3.91-4.82)	1.53 (1.38-1.71)	3.89 (3.63-4.14)	0.76 (0.60-0.95)
Moderately reduced LVEF (30%-39%)	6048	6.58	5.68 (5.12-6.31)	1.85 (1.68-2.05)	5.36 (5.07-5.64)	1.31 (1.13-1.50)
Severely reduced LVEF (<30%)	4185	8.34	7.34 (6.56-8.21)	2.35 (2.09-2.63)	7.12 (6.77-7.46)	2.24 (2.02-2.49)
Model 3: heart failure defined by presence of recent symptoms[d]						
Without heart failure	561 738	1.22	1 [Reference]	1 [Reference]	Reference	Reference
Heart failure						
Asymptomatic	42 091	4.84	4.10 (3.90-4.31)	1.53 (1.44-1.63)	3.62 (3.50-3.74)	0.74 (0.63-0.87)
Symptomatic	5906	10.11	9.07 (8.31-9.90)	2.37 (2.14-2.63)	8.89 (8.59-9.17)	2.37 (2.06-2.57)

Abbreviations: LVEF, left ventricular ejection fraction; OR, odds ratio.

[a] Multivariable mixed-effects logistic regression model adjusted for sex, age, body mass index, alcohol consumption, comorbidities (hypertension, atrial fibrillation, diabetes, coronary artery disease, stroke, chronic obstructive pulmonary disease, peripheral vascular disease), preoperative creatinine level, preoperative hematocrit level, American Society of Anesthesiologists class and surgical complexity, and Veterans Affairs facility.

[b] Calculated using the following formula, with average adjusted predicted probabilities for each group calculated via the corresponding regression model (see Table 2, footnote a): (average adjusted predicted probability in exposed) −(average predicted probability in unexposed).

[c] The OR compares patients with heart failure with the given left ventricular ejection fraction with patients without heart failure. Does not include 1410 patients with missing LVEF. *P* value for trend <.001.

[d] Classified per the American College of Surgeons National Surgical Quality Improvement Program and Veterans Affairs Surgical Quality Improvement Program definitions of symptomatic congestive heart failure: the presence of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, increased jugular venous distension, or pulmonary rales within 30 days of surgery.

reduced systolic function (LVEF, 30%-39%; 1034 [17.1%] with symptoms, 5014 [82.9%] without symptoms), and 4185 patients (8.7%) had severely reduced systolic function (LVEF, <30%; 872 [20.8%] with symptoms, 3313 [79.2%] without symptoms). Echocardiograms were not available for 1410 patients (2.9%).

Review of pharmacy records suggested optimal medical management for the majority of patients with heart failure, with 91.7% receiving a β-blocker and 92.3% receiving an angiotensin-converting enzyme (ACE) inhibitor (eTable 2 in the Supplement). Of patients with heart failure, 34.6% received a potassium-sparing diuretic.

Distribution of Procedures Performed

Patients with heart failure underwent more complex procedures than patients without heart failure (Table 1). Procedures performed on patients with heart failure were divided between standard (52.8%) and intermediate or complex (47.2%) levels, whereas patients without heart failure more commonly received standard level of complex procedures (60.8% standard, 39.2% intermediate or complex; $P < .001$). Patients with heart failure also underwent more inpatient procedures than those without heart failure (59.3% vs 40.0%; $P < .001$).

Postoperative Mortality

The crude 90-day postoperative mortality risk among patients with a history of heart failure was 5.49% (2635 90-day deaths) compared with 1.22% (6881 90-day deaths) among patients without heart failure. Heart failure was significantly associated with postoperative mortality after multivariable adjustment for clinical, demographic, and surgical factors (adjusted absolute RD, 1.03%; 95% CI, 0.91-1.15; adjusted OR, 1.67; 95% CI, 1.57-1.76; **Table 2**). The risk of postoperative mortality progressively increased with decreasing systolic function (*P* for trend <.001), with all ejection fraction groups having a higher risk of postoperative mortality than patients without heart failure. Compared with patients without heart failure, patients who had either asymptomatic (2038 deaths [4.84%]; adjusted absolute RD, 0.74%; 95% CI, 0.63%-0.87%; adjusted OR, 1.53; 95% CI, 1.44-1.63) or symptomatic (597 deaths [10.11%]; adjusted absolute RD, 2.37%, 95% CI, 2.06%-2.57%; adjusted OR, 2.37; 95% CI, 2.14-2.63) heart failure had a higher risk of postoperative mortality. The E-value sensitivity analysis for unmeasured confounding was calculated for the adjusted OR for patients with symptomatic heart failure (eTable 10 in the Supplement). The adjusted OR point estimate of 2.37 for the risk of postoperative mortality associated with symptomatic heart failure corresponds to an

Table 3. Adjusted Odds Ratios (ORs) and Risk Differences of 90-Day Postoperative Mortality Between Patients With and Without Heart Failure Stratified by Surgical Complexity

	No. of Patients		Mortality, %					
Complexity	Heart Failure	Without Heart Failure	Heart Failure	Without Heart Failure	Crude Absolute Risk Difference (95% CI), %	Adjusted Absolute Risk Difference (95% CI), %[a]	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
Standard[c]	25 327	341 749	4.62	0.66	3.96 (3.84-4.08)	1.29 (1.22-1.37)	7.31 (6.80-7.85)	2.35 (2.15-2.58)
Intermediate	21 509	209 022	6.26	1.89	4.37 (4.16-4.58)	1.69 (1.48-1.94)	3.46 (3.25-3.69)	1.79 (1.65-1.92)
Complex	1161	10 967	10.34	6.19	4.15 (2.65-5.64)	1.80 (0.08-3.60)	1.74 (1.42-2.14)	1.29 (1.02-1.63)

[a] Calculated using the following formula, with average adjusted predicted probabilities for each group calculated via the corresponding regression model (See Table 3, footnote b): (average adjusted predicted probability in exposed) −(average predicted probability in unexposed).

[b] Multivariable mixed-effects logistic regression model adjusted for sex, age, body mass index, alcohol consumption, comorbidities (hypertension, atrial fibrillation, diabetes, coronary artery disease, stroke, chronic obstructive pulmonary disease, peripheral vascular disease), preoperative creatinine, preoperative hematocrit, American Society of Anesthesiologists class and surgical complexity, and Veterans Affairs facility.

[c] *P* value for heart failure × surgical complexity interaction term <.001.

E-value of 4.17, and for the confidence interval value closest to the null, 2.14, the E-value was 3.70.

All patients with a history of heart failure, regardless of systolic function or presence of heart failure symptoms, had a higher risk of postoperative mortality compared with patients without heart failure (eTable 3 in the Supplement). Patients with a history of heart failure, without symptoms and with preserved LVEF (n = 25 891) had a crude 90-day post-operative mortality risk of 4.42% (adjusted absolute RD, 0.66%; 95% CI, 0.54%-0.79%; adjusted OR, 1.46, 95% CI, 1.35-1.57) and patients with heart failure, symptoms of heart failure, and severely reduced LVEF (n = 872) experienced a crude risk of 14.91% (adjusted absolute RD, 5.87%; 95% CI, 5.30%-6.44%; OR, 3.67; 95% CI, 2.98-4.52).

The association between heart failure and postoperative mortality was similar at 30-day, 90-day, and 1-year time points (eTables 4 and 5 in the Supplement).

Both crude mortality risks and the heart failure-mortality association differed significantly between levels of surgical complexity (*P* < .001 for the surgical complexity × heart failure interaction, **Table 3**). The crude 90-day postoperative mortality for patients with heart failure increased from 4.62% for standard complexity operations to 10.34% for complex procedures. For patients without heart failure, crude 90-day postoperative mortality increased from 0.66% to 6.19% (from standard to complex procedures). The adjusted absolute RD between patients with and without heart failure was 1.29% (95% CI, 1.22%-1.37%) for standard procedures, 1.69% (95% CI, 1.48%-1.94%) for intermediate procedures, and 1.80% (95% CI, 0.08%-3.60%) for complex procedures.

The attributable risk fraction of heart failure on 90-day postoperative mortality was highest among patients undergoing standard procedures (48%) and lowest among patients undergoing complex procedures (15%).

In a post hoc secondary analysis, patients with heart failure had a higher risk of postoperative complications (including cardiac arrest and major bleed) and longer length of stay than patients without heart failure (eTables 6 and 7 in the Supplement).

A sensitivity analysis replacing imputation of missing laboratory values with a complete case analysis did not significantly change the results (eTable 8 in the Supplement), nor did a propensity score-adjusted sensitivity analysis (eTable 9 in the Supplement).

Discussion

In this retrospective cohort study of more than 600 000 veterans, patients with heart failure, including both those with symptoms and those with no symptoms and preserved systolic function, had a higher risk of 90-day postoperative mortality than did patients without heart failure.

Heart failure is an important marker for having a high risk of postoperative mortality. In general, symptomatic patients had a higher risk than did asymptomatic patients. Low ejection fraction was associated with greater postoperative mortality with the mortality risk increasing as the ejection fraction decreased. Multivariable regression greatly attenuated the apparent risk of heart failure on postoperative mortality suggesting that heart failure is a marker for a constellation of comorbidities that patients with heart failure tend to have, all of which contribute to the elevated risk. Heart failure itself has a relatively small effect as an independent risk factor of postoperative mortality.

One interpretation of these findings is that patients with heart failure, especially those with symptoms or very low ejection fractions, should be counseled regarding their higher risk of postoperative surgical mortality. Although optimizing their cardiac function should be pursued, all other associated modifiable risk factors that might contribute to postoperative mortality should also be optimized since heart failure by itself has a relatively small association with mortality.

A previous study of 174 patients[11] showed that left ventricular systolic dysfunction was associated with greater postoperative mortality beyond the baseline risk associated with heart failure alone. However, this association was only observed for severely reduced LVEF (<30%). The current study, which was much larger, was able to demonstrate that the risk of postoperative mortality progressively increased with decreasing systolic function. Preoperative evaluation of a patient's ejection fraction may be useful in decision-making for all patients with heart failure, not only those with severely reduced LVEF or heart failure symptoms.

Left ventricular systolic dysfunction may also be useful if included in surgical risk prediction models, especially when evaluating asymptomatic patients.

Patients with heart failure in this study underwent more intermediate- and complex-level procedures and fewer standard-level procedures than those without heart failure. This pattern might be explained by 2 factors. First, the patients with heart failure were generally older and had more medical comorbidities than the patients without heart failure. These patients may have required more complex procedures (such as pancreaticoduodenectomy or kidney transplant) to address their comorbid conditions (such as cancer or renal failure). Fewer standard-level procedures were performed on patients with heart failure, and this may result from reluctance among clinicians to pursue surgery because of the risks associated with heart failure. Given the known risks of noncardiac surgery for patients with heart failure, clinicians may have recommended against simple, standard-level procedures that were more likely to be truly elective, such as a hernia, or treatable with nonsurgical options, such as an uncomplicated appendectomy, than an intermediate- or complex-level procedure, such as a colectomy or an esophagectomy.

Various perioperative factors may have contributed to the higher postoperative mortality observed for patients with heart failure even in low-complexity procedures. There may be risk associated with general anesthesia among patients with heart failure attributable to intraoperative or postoperative hypotension independent of surgical complexity level. With heart failure, even minor postoperative complications may be poorly tolerated reducing long-term survival.[33]

Limitations

This study had several limitations. First, by the nature of the inclusion criteria, all patients in this study were deemed "fit for surgery" by a physician. Data about patients who were considered for but did not receive surgery were not available, potentially resulting in selection bias and limiting the generalizability of this study's findings. Second, this analysis was not able to compare baseline mortality rates not attributable to surgery because all patients in this study received surgery. It is especially important in this patient population to acknowledge that immediate postoperative issues and complications affect long-term survival beyond the perioperative period.[33]

Third, as with any observational study, there is a risk of unmeasured confounding factors that may, if accounted for, negate the apparent contribution of heart failure as an independent risk factor for postoperative mortality. E-values were calculated as a sensitivity analysis to determine the likelihood that an unmeasured confounder could exist that would negate the observed relationship between heart failure and postoperative mortality. This seems unlikely because the range of point estimates for the ORs for all the known risk factors available in the data extended from 0.96 to 1.53 (eTable 11 in the Supplement). The E-values for the confidence intervals closest to the null for the adjusted ORs for the association between heart failure (overall), the presence of heart failure symptoms, and ejection fraction ranged from 2.04 to 3.70 (eTable 10 in the Supplement). An unmeasured confounder would necessarily have an OR exceeding these values, a possibility seemingly remote because the ORs for all measured, known risk factors for postoperative mortality fell short of the E-values found in eTable 10 in the Supplement.

Fourth, the generalizability of this study is limited because it was a VA population that was examined. There were relatively few women in the study cohort. However, although the percentage of women in this study was relatively small, the absolute number of female patients with heart failure included in this study was much larger than prior, similar studies.[34]

Conclusions

Among patients undergoing elective noncardiac surgery, heart failure with or without symptoms was significantly associated with 90-day postoperative mortality. These data may be helpful in preoperative discussions with patients with heart failure undergoing noncardiac surgery.

ARTICLE INFORMATION

Accepted for Publication: January 10, 2019.

Author Contributions: Mr Lerman and Dr Wren had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Lerman, Assimes, Heidenreich, Wren.
Acquisition, analysis, or interpretation of data: Lerman, Popat.
Drafting of the manuscript: Lerman.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Lerman, Popat.
Obtained funding: Lerman.
Administrative, technical, or material support: Assimes, Wren.
Supervision: Assimes, Wren.

Conflict of Interest Disclosures: None reported.

Funding/Support: Mr Lerman was supported by a National Institutes of Health, Center for Advancing Translational Science, Clinical and Translational Science Award (TL1TR001084 and UL1TR001085).

Role of the Funder/Sponsor: The sponsor had no role in the design and conduct of the study; management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. The sponsor did not have the right to veto publication.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government.

Additional Contributions: We thank Alexander Sox-Harris, PhD (Palo Alto Veterans Affairs Health Care System; Department of Surgery, Stanford School of Medicine), Laura Graham, PhD (Department of Surgery, Stanford School of Medicine), and Amber Trickey, PhD (Stanford Surgery Policy Improvement Research and Education Center) for contributions to the collection and management of the data and Robert Lerman, MD, for contributions to preparation and review of the manuscript. They did not receive compensation for their roles in the study.

REFERENCES

1. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100(10):1043-1049. doi:10.1161/01.CIR.100.10.1043

2. Benjamin EJ, Blaha MJ, Chiuve SE, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10):e146-e603. doi:10.1161/CIR.0000000000000485

3. Hammill BG, Curtis LH, Bennett-Guerrero E, et al. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology*. 2008; 108(4):559-567. doi:10.1097/ALN.0b013e31816725ef

4. Hanninen M, McAlister FA, Bakal JA, van Diepen S, Ezekowitz JA. Neither diabetes nor glucose-lowering drugs are associated with mortality after noncardiac surgery in patients with coronary artery disease or heart failure. *Can J Cardiol*. 2013;29(4):423-428. doi:10.1016/j.cjca.2012.07.004

5. Hernandez AF, Whellan DJ, Stroud S, Sun JL, O'Connor CM, Jollis JG. Outcomes in heart failure patients after major noncardiac surgery. *J Am Coll Cardiol*. 2004;44(7):1446-1453. doi:10.1016/j.jacc.2004.06.059

6. van Diepen S, Bakal JA, McAlister FA, Ezekowitz JA. Mortality and readmission of patients with heart failure, atrial fibrillation, or coronary artery disease undergoing noncardiac surgery: an analysis of 38 047 patients. *Circulation*. 2011;124(3): 289-296. doi:10.1161/CIRCULATIONAHA.110.011130

7. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg. 2013;217(5):833-42.e1-3.

8. Muntwyler J, Abetel G, Gruner C, Follath F. One-year mortality among unselected outpatients with heart failure. *Eur Heart J*. 2002;23(23):1861-1866. doi:10.1053/euhj.2002.3282

9. Rostagno C, Galanti G, Comeglio M, Boddi V, Olivo G, Gastone Neri Serneri G. Comparison of different methods of functional evaluation in patients with chronic heart failure. *Eur J Heart Fail*. 2000;2(3):273-280. doi:10.1016/S1388-9842(00)00091-X

10. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J*. 2012;33(14):1750-1757. doi:10.1093/eurheartj/ehr254

11. Healy KO, Waksmonski CA, Altman RK, Stetson PD, Reyentovich A, Maurer MS. Perioperative outcome and long-term mortality for heart failure patients undergoing intermediate- and high-risk noncardiac surgery: impact of left ventricular ejection fraction. *Congest Heart Fail*. 2010;16(2):45-49. doi:10.1111/j.1751-7133.2009.00130.x

12. Xu-Cai YO, Brotman DJ, Phillips CO, et al. Outcomes of patients with stable heart failure undergoing elective noncardiac surgery. *Mayo Clin Proc*. 2008;83(3):280-288. doi:10.4065/83.3.280

13. Flu WJ, van Kuijk JP, Hoeks SE, et al. Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. *Anesthesiology*. 2010;112(6):1316-1324. doi:10.1097/ALN.0b013e3181da89ca

14. Khuri SF, Daley J, Henderson W, et al. The Department of Veterans Affairs' NSQIP peer-controlled program for the measurement and enhancement of the quality of surgical care. *Ann Surg*. 1998;228(4):491-504. doi:10.1097/00000658-199810000-00006

15. Massarweh NN, Kaji AH, Itani KMF. Practical guide to surgical data sets: Veterans Affairs Surgical Quality Improvement Program (VASQIP). *JAMA Surg*. 2018;153(8):768-769. doi:10.1001/jamasurg.2018.0504

16. Patterson OV, Freiberg MS, Skanderson MJ, Fodeh S, Brandt CA, DuVall SL. Unlocking echocardiogram measurements for heart disease research through natural language processing. *BMC Cardiovasc Disord*. 2017;17(1):151. doi:10.1186/s12872-017-0580-8

17. Garvin JH, DuVall SL, South BR, et al. Automated extraction of ejection fraction for quality measurement using regular expressions in unstructured information management architecture (UIMA) for heart failure. *J Am Med Inform Assoc*. 2012;19(5):859-866. doi:10.1136/amiajnl-2011-000535

18. Floyd JS, Blondon M, Moore KP, Boyko EJ, Smith NL. Validation of methods for assessing cardiovascular disease using electronic health data in a cohort of veterans with diabetes. *Pharmacoepidemiol Drug Saf*. 2016;25(4):467-471. doi:10.1002/pds.3921

19. Borzecki AM, Wong AT, Hickey EC, Ash AS, Berlowitz DR. Identifying hypertension-related comorbidities from administrative data: what's the optimal approach? *Am J Med Qual*. 2004;19(5):201-206. doi:10.1177/106286060401900504

20. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. *PLoS One*. 2014;9(8):e104519. doi:10.1371/journal.pone.0104519

21. Szeto HC, Coleman RK, Gholami P, Hoffman BB, Goldstein MK. Accuracy of computerized outpatient diagnoses in a Veterans Affairs general medicine clinic. *Am J Manag Care*. 2002;8(1):37-43.

22. Chronic conditions data warehouse: condition categories. https://www.ccwdata.org/web/guest/condition-categories. Published 2018. Accessed April 22, 2018.

23. Left ventricular ejection fraction assessment in the outpatient setting. American College of Cardiology web page. https://www.acc.org/tools-and-practice-support/clinical-toolkits/heart-failure-practice-solutions/left-ventricular-ejection-fraction-lvef-assessment-outpatient-setting. Published 2018. Accessed April 30, 2018.

24. Turrentine FE, Sohn MW, Jones RS. Congestive heart failure and noncardiac operations: risk of serious morbidity, readmission, reoperation, and mortality. *J Am Coll Surg*. 2016;222(6):1220-1229. doi:10.1016/j.jamcollsurg.2016.02.025

25. Petzel RA. Surgical complexity initiative. Institute of Medicine Commentaries. https://nam.edu/wp-content/uploads/2015/06/VSRT-Surgical-Complexity-Initiative.pdf. Published 2012. Accessed April 28, 2018.

26. Department of Veterans Affairs Office of Inspector General. A review of facility capabilities where veterans received complex surgical care. https://www.va.gov/oig/54/reports/VAOIG-10-02302-225.pdf. No. 10-02302-225. Published July 14, 2011. Accessed April 28, 2018.

27. Maile MD, Engoren MC, Tremper KK, Jewell E, Kheterpal S. Worsening preoperative heart failure is associated with mortality and noncardiac complications, but not myocardial infarction after noncardiac surgery: a retrospective cohort study. *Anesth Analg*. 2014;119(3):522-532. doi:10.1213/ANE.0000000000000116

28. Koo CY, Hyder JA, Wanderer JP, Eikermann M, Ramachandran SK. A meta-analysis of the predictive accuracy of postoperative mortality using the American Society of Anesthesiologists' physical status classification system. *World J Surg*. 2015;39(1):88-103. doi:10.1007/s00268-014-2783-9

29. Durstenfeld MS, Ogedegbe O, Katz SD, Park H, Blecker S. Racial and ethnic differences in heart failure readmissions and mortality in a large municipal healthcare system. *JACC Heart Fail*. 2016; 4(11):885-893. doi:10.1016/j.jchf.2016.05.008

30. Jayatillake RV, Sooriyarachchi MR, Senarathna DLP. Adjusting for a cluster effect in the logistic regression model: an illustration of theory and its application. *J Natl Sci Found Sri Lanka*. 2011;39(3): 211-218.

31. Haneuse S, VanderWeele TJ, Arterbum D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies [published online January 24, 2019]. *JAMA*. doi:10.1001/jama.2018.21554

32. Mathur MB, Ding P, Riddell CA, VanderWeele TJ. Web site and R package for computing E-values. *Epidemiology*. 2018;29(5):e45-e47. doi:10.1097/EDE.0000000000000864

33. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Participants in the VA National Surgical Quality Improvement Program. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242(3):326-341.

34. Aimo A, Vergaro G, Barison A, et al. Sex-related differences in chronic heart failure. *Int J Cardiol*. 2018;255:145-151. doi:10.1016/j.ijcard.2017.10.068