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History of Depression and Increased Risk of Sternal Wound Infection After Cardiothoracic Surgery: A Novel and Potentially Modifiable Risk Factor

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Background. Sternal wound infection (SWI) is a leading cause of postoperative disease and death; the risk factors for SWI remain incompletely understood. The goal of the current study was to investigate the relationship between a preoperative history of depression and the risk of SWI after cardiothoracic surgery.

Methods. Among patients undergoing cardiothoracic surgery in a major academic medical center between 2007 and 2012, those in whom SWI developed (n = 129) were matched, by date of surgery, with those in whom it did not (n = 258). Multivariable logistic regression was used to examine the strength of relationships between risk factors and development of infection. History of depression was defined as a composite variable to increase the sensitivity of detection.

Results. History of depression as defined by our composite variable was associated with increased risk of SWI (adjusted odds ratio, 2.4; 95% confidence interval, 1.2–4.7; $P = .01$). *Staphylococcus aureus* was the most common organism isolated.

Conclusions. History of depression was associated with increased risk of SWI. Future prospective studies are warranted to further investigate this relationship. Depression is highly treatable, and increased efforts to identify and treat depression preoperatively may be a critical step toward preventing infection-related disease and death.

Keywords. cardiothoracic surgery; depression; sternal wound infection.

Sternal wound infection (SWI) after sternotomy is a serious complication of cardiothoracic surgery and is associated with increased morbidity and mortality rates, length of stay, and cost of care [1–4]. Infections range in severity from superficial incisional infections to mediastinitis and sternal osteomyelitis. Superficial SWIs develop in approximately 2%–6% of patients after cardiothoracic surgery [5–8], and the average incidence of mediastinitis after sternotomy is <2% [9–11]. Although the risk factors for SWI are heavily debated, obesity, diabetes, prolonged duration of surgery, use of bilateral internal mammary artery grafts, and reoperation have been repeatedly identified as such [4, 7, 12, 13].

Major depression affects >20% of patients undergoing sternotomy for coronary artery bypass grafting (CABG) [14, 15]. It more than doubles the morbidity and mortality risks in the first 12 months after CABG, although the mechanism by which depression may affect CABG outcomes is not clear. Depression is also strongly linked to poor cardiovascular outcomes in patients with coronary disease and congestive heart failure [15–20].

An association between depression and infection has been well documented in various domains. For instance, hospitalized older adults with depression have higher rates of *Clostridium difficile* infection than those without depression [21]. Depression among patients undergoing peritoneal dialysis is associated with increased risk of peritonitis [22]. In a retrospective study of almost 50 000 college students, those with depression had an increased risk of bronchitis, ear infection, sinus infection, and strep throat [23]. Depression has been linked with increased risk of pneumococcal pneumonia, septicemia, and meningitis, compared with those without depression [24]. Moreover, it has been linked specifically to infection in patients undergoing cardiac surgery; patients with a history of depression who undergo cardiothoracic surgery for placement of a ventricular assist device (VAD; heart pump) are significantly more likely to have VAD infection than those without a history of depression (adjusted hazard ratio, 2.8; $P = .007$) [25]. SWI is a possible pathway through which depression could affect cardiothoracic surgery outcomes.

To our knowledge, however, no prior study has examined the relationship between preoperative depression and risk of SWI. To begin to fill this gap, the present case-control study

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investigated the relationship between a preoperative history of depression and risk of SWI after cardiothoracic surgery.

METHODS

Study Population and Ethics Statement

Case patients were identified by the Department of Infection Prevention and Control, which maintains a list of all patients in whom surgical site infection develops. Case patients included all patients aged ≥18 years in whom SWI developed after they underwent sternotomy or thoracotomy for CABG, heart valve repair or replacement, aortic root surgery, or coronary artery unroofing at the New York–Presbyterian Hospital Milstein Hospital Building between 2007 and 2012. Surgery could include >1 procedure. Postdischarge surveillance for infection included a 6-week follow-up appointment with the attending surgeon. A Department of Infection Prevention and Control case patient either met the Centers for Disease Control and Prevention's National Healthcare Safety Network guidelines for surgical site infection [26] or had a clinical picture consistent with this diagnosis, as determined by the infectious disease physician hospital epidemiologist and attending cardiothoracic surgeon.

To identify potential controls, the Department of Circulatory Physiology provided a list of all patients who underwent the same cardiothoracic surgical procedures at the Milstein Hospital Building during the same time period; the list was generated via a data warehouse query using search terms to capture each included surgery type. Patients without SWI were potential controls. Controls were matched to case patients according to date of surgery (within 45 days) to minimize the influence of potential temporal infection trends within the hospital. A computerized selection algorithm randomly selected 2 controls for each case patient. Exclusion criteria for case patients and controls included age <18 years, orthotopic heart transplantation or VAD placement as the index operation, pregnancy at the time of surgery, death within 5 days of surgery, and surgical site infection unrelated to the sternotomy or thoracotomy (ie, soft-tissue infection from saphenous vein harvesting). The incidence of cardiothoracic surgical site infection (excluding heart transplant recipients) in the Milstein Hospital Building during the study period ranged from 1.0% to 2.2% and decreased over time. This study was approved by the Institutional Review Board at Columbia University Medical Center (IRB-AAAK9857).

Data Collection

Data were collected retrospectively by reviewing the electronic medical record. Data provided by outside hospitals before the study began were also included, but further information was not solicited from outside hospitals. Variables included demographic data, medical and psychiatric history, medications, laboratory values, hospital course, operative details, and characteristics of infection.

Definition of Depression

Dedicated screening for depression had not been performed preoperatively. In our exploratory study, a composite definition of depression was therefore created to improve the likelihood of detecting a preoperative history of depression. Patients were considered to have a history of depression if they had (1) a recorded preoperative diagnosis of depression in their medical record, (2) a recorded preoperative *International Classification of Diseases, Ninth Revision,* code for depression in their medical record, (3) a self-reported "depressed" mood recorded on the review of systems section of the preoperative cardiothoracic surgery consult note, or (4) use of either a first-line antidepressant or >1 antidepressant at the time of surgery or within the year before surgery, as recorded in the medical record. Bupropion, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors were considered first-line antidepressants. This composite variable was created a priori with the primary hypothesis that a history of depression, as defined by this composite variable, would be associated with increased risk of SWI. Secondary a priori analyses were planned to assess whether the individual components of the composite variable were also associated with increased risk of SWI.

Statistical Analyses

Descriptive statistics were generated for demographic variables, medical history, depression history, laboratory values, and intraoperative variables. In the univariate analysis, categorical data were compared between case patients and controls using Fisher exact or χ^2 tests, as appropriate. Continuous variables were compared using *t* or Wilcoxon rank sum tests. A multivariable model was created to examine the joint effect of the potential risk factors on infection. All potential risk factors with a *P* value <.10 in the univariate analysis or that were thought likely to influence infection risk (ie, tobacco use) were considered for a modified forward stepwise selection procedure, in which insignificant variables are removed from the model before adding a variable at each step.

We used a *P* value cutoff <.10 for removing variables in the final model selection procedure. Each addition or deletion of a variable to or from a model is a separate step in the selection process; at each step, a new model is fitted. This approach defines an a posteriori order based on the relative uniqueness of the variables in the sample. In addition, sex and age were kept in the final model. Rubin's multiple imputation method with 11 repeated imputations was used to impute the missing data to conduct the sensitivity analysis. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) and *P* values were generated. Variance inflation factors were calculated and were all approximately 1, indicating there was not significant multicolinearity. SAS software version 9.3 (SAS Institute) was used to perform all analyses, and differences were considered statistically significant at $P < .05$.

RESULTS

Characteristics of Study Participants

The study population comprised 387 patients in total (129 case patients and 258 controls), ranging in age from 22 to 93 years. The mean age (standard deviation) was 67 (13.2) years for case patients and 69.5 (12.7) years for controls. A total of 386 sternotomies and 1 thoracotomy were performed by 12 surgeons. Operations could incorporate >1 procedure and included 221 CABGs (90 in case patients and 131 in controls), 248 valve and/or aortic root operations (69 in case patients and 179 in controls), and 2 coronary artery unroofing procedures (both in controls). Patients received a chlorhexidine wash according to standard preoperative procedure. Thirty-five patients had a recorded preoperative nares screen for methicillin-resistant *Staphylococcus aureus*; only 1 (a control) had a positive screen. Antimicrobial prophylaxis guidelines were issued in March 2007; cefazolin was the primary antimicrobial prophylaxis recommended, with vancomycin as an alternative agent. A stewardship team was involved in creating the guidelines.

The median time in the hospital before surgery was 1 day (interquartile range, 4 days) and did not differ between case patients and controls ($P = .16$), and the median duration of total hospital admission was 10 days (11 days), significantly longer for case patients than for controls (13 vs 9.5 days; $P = <.001$). One hundred forty-seven patients required reoperations (for sternal debridement, reoperative valve surgery, exploration for bleeding, or pericardial window creation, among other reasons), and case patients were more likely to do so (98 vs 49; $P < .001$). Sternal washout or debridement was the surgical indication for 90 of the 98 case patients who underwent reoperation. Of the 129 case patients, SWI developed in 30 before discharge. Patients in whom infection developed were more likely to be readmitted to the hospital and to the intensive care unit (both $P < .001$). Of the 105 case patients who were readmitted to the hospital, 93 were readmitted for SWI. Twenty-two patients died (14 case patients and 8 controls; $P = .003$).

Of 49 patients who took antidepressants at the time of surgery or within the previous year, 32 took a selective serotonin reuptake inhibitor, 10 an atypical antidepressant, 7 a tricyclic antidepressant, 3 a selective norepinephrine reuptake inhibitor, and 1 a monoamine oxidase inhibitor; 1 did not have the type of antidepressant recorded, and 5 took >1 antidepressant. Seven of the 10 persons using an atypical antidepressant took bupropion. Bupropion can also be prescribed for smoking cessation, so the tobacco use histories of these 7 patients were examined; 5 were never smokers, 1 was a former smoker who had another indicator of depression, and 1 (a control) was a current smoker who was taking bupropion for an unknown indication.

Univariate Analysis

Study patients are described in Table 1. Age and sex did not significantly differ between case patients and controls ($P = .06$ and $P = .91$, respectively); 83 (64.3%) case patients and 168 (65.1%) controls were male. Ethnicity (Hispanic versus non-Hispanic), race, marital status, employment status, disability status, and living situation similarly did not differ between case patients and controls. Case patients were significantly more likely than controls to have a history of diabetes mellitus ($P = .04$), peripheral vascular disease ($P = .007$), hypertension ($P = .006$), chronic obstructive pulmonary disease ($P = .002$), myocardial infarction ($P = .03$), or obesity ($P = .005$).

A history of depression, as defined by the composite variable, was independently associated with infection ($P = .01$). The individual components of the composite variable were assessed in univariate analysis as well; as shown in Table 2, a depressed mood reported on the review of systems of the preoperative cardiac surgery consult note ($P = .03$) and use of a first-line antidepressant at the time of surgery ($P = .05$) or within the year before surgery ($P = .03$) were independently associated with increased risk of infection. A recorded diagnosis of depression in the medical history was not independently associated with increased risk of infection ($P = .70$). Although only 7 patients reported a depressed mood on the preoperative review of systems, 6 of them went on to have SWI, compared with 94 of the 291 who did not report a depressed mood. (The review of systems was not recorded in 90 patients).

Baseline laboratory characteristics are listed in Table 3. Case patients were significantly more likely than controls to have a higher body mass index ($P < .001$) and postoperative glucose level ($P = .02$). Overall, perioperative glucose control was suboptimal; of the 131 patients with diabetes who had available preoperative and postoperative glucose data, 76 had a perioperative glucose level >180 mg/dL.

Among intraoperative factors (shown in Table 4), bilateral internal mammary artery use was associated with increased risk of infection ($P = .001$). Undergoing CABG was associated with SWI (aOR, 2.3; 95% CI, 1.4–3.7; $P = .001$), and undergoing valve and/or aortic root surgery was not (0.5; .3–.8; $P = .003$). More controls than case patients underwent an operation that included a prosthetic material ($P = .01$). Although the majority of case patients and controls received intraoperative antibiotic prophylaxis with cefazolin, more controls than case patients received prophylaxis with vancomycin and gentamicin (compared with vancomycin alone or cefazolin alone) ($P = .03$).

Findings from the sensitivity analysis via the multiple imputation method for missing data were very similar to those obtained by analyzing only the observed data; this suggests that bias due to missingness, if any, may be negligible. We report the results without imputation so that the aORs obtained from the subsequent multivariable analysis were consistent with the frequencies and proportions shown in the tables.

Multivariable Analysis

In the multivariable analysis, history of depression, as defined by the composite variable, was independently associated with

Table 1. Characteristics of Study Patients

Demographic Factors and Medical History	Patients, No. (%)[a]		*P* Value
	Case Patients (n = 129)	Controls (n = 258)	
Age, mean (SD), y	67 (13.2)	69.5 (12.7)	.06
Male sex	83 (64.3)	168 (65.1)	.91
Hispanic ethnicity	25 (22.5)	28 (14.4)	.11
Race			
White	91 (84.3)	189 (82.5)	.73
Black	10 (9.3)	24 (10.5)	
Asian	6 (5.6)	15 (6.6)	
Other	1 (0.9)	1 (0.4)	
Marital status			
Single	14 (11.2)	21 (8.4)	.65
Married	81 (64.8)	169 (67.9)	
Separated	3 (2.4)	3 (1.2)	
Divorced	9 (7.2)	12 (4.8)	
Widowed	18 (14.4)	44 (17.6)	
Employment status			
Employed	37 (29.1)	66 (27.0)	.37
Unemployed	13 (10.2)	19 (7.8)	
Homemaker	2 (1.6)	2 (0.8)	
Student	1 (0.8)	0 (0)	
Retired	74 (58.3)	157 (64.3)	
Disability status			
Not disabled or receiving SSI	104 (83.2)	218 (91.2)	.19
Disabled, receiving SSI	15 (12)	12 (5.0)	
Disabled, not receiving SSI	5 (4)	5 (2.1)	
Not disabled, receiving SSI[b]	1 (0.8)	4 (1.7)	
Living situation			
Alone	24 (19.2)	47 (19.6)	.19
With family	96 (76.8)	178 (74.2)	
With health aide	4 (3.2)	1 (0.4)	
In long-term care facility	0 (0)	6 (2.5)	
Homeless	0 (0)	1 (0.4)	
With a friend	1 (0.8)	5 (2.1)	
Other	0 (0)	2 (0.8)	
Tobacco use			
Never smoker	57 (44.9)	117 (46.8)	.93
Current smoker	13 (10.2)	19 (7.6)	
Past smoker	57 (44.9)	114 (45.6)	
Alcohol abuse			
Never	116 (93.6)	223 (94.1)	.96
Currently	4 (3.2)	6 (2.5)	
Past	4 (3.2)	8 (3.4)	
Diabetes mellitus	58 (47.9)	93 (36.2)	.04
Chronic kidney disease	33 (27.5)	50 (19.6)	.09
Peripheral vascular disease	28 (23.9)	29 (11.8)	.007
Infection <30 d before surgery	23 (17.8)	41 (15.9)	.64
Hypertension	116 (90.6)	202 (78.3)	.006
Hyperlipidemia	100 (81.3)	194 (76.7)	.36
Heart failure[c]	60 (46.5)	99 (38.4)	.14
COPD	25 (21.4)	28 (11.0)	.002
Cirrhosis	4 (3.4)	3 (1.2)	.23
Stroke	14 (11.9)	19 (7.4)	.13
Dialysis	5 (3.9)	6 (2.3)	.40
Previous myocardial infarction	48 (38.7)	69 (27.1)	.03
Previous sternotomy	17 (13.2)	49 (19.1)	.17
Dual antiplatelet therapy	23 (17.97)	44 (17.25)	.85
Statin use	85 (65.9)	169 (66.3)	.97
Immunosuppression[d]	8 (6.2)	9 (3.5)	.24
Obesity[e]	59 (46.5)	78 (30.7)	.005

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation; SSI, Supplemental Security Income.

[a]Data represent No. (%) of patients unless otherwise specified. Data were missing for Hispanic ethnicity in 81 patients, race in 50, marital status in 13, employment status in 16, disability status in 23, living situation in 22, tobacco use in 10, alcohol abuse in 26, diabetes in 9, chronic kidney disease in 12, peripheral vascular disease in 24, hypertension in 1, hyperlipidemia in 11, heart failure in 26, COPD in 16, cirrhosis in 14, stroke in 13, dialysis in 1, previous myocardial infarction in 8, previous sternotomy in 1, dual antiplatelet therapy in 3, statin use in 3, immunosuppression in 2, and obesity in 7.

[b]Patients >65 years old and meeting financial criteria for SSI.

[c]Defined by a recorded history of congestive heart failure or a left ventricular ejection fraction <40%.

[d]Taking immunosuppressive medication or known to have human immunodeficiency virus.

[e]Defined by body mass index >30 kg/m^2.

the development of SWI (aOR, 2.4; 95% CI, 1.2–4.7; P = .01). The risk associated with depression was stronger than that associated with all other medical comorbid conditions (Table 5).

Characteristics of Infections

Of the 129 infections, 23 were superficial SWIs, 27 were deep SWIs, and 79 were organ/space infections. Of the 28 case patients with history of depression, as defined by the composite variable, 5 had a superficial SWI, 8 had a deep SWI, and 15 had an organ/space infection.

Thirty-eight infections were polymicrobial, and 5 were culture negative. *S. aureus* was the most common organism isolated (n = 55), followed by other staphylococcal species (n = 34), *Klebsiella* spp. (n = 21), *Pseudomonas* spp. (n = 13), and *Enterococcus* spp. (n = 13). Of the *S. aureus* isolates, 33 were methicillin susceptible, 21 were methicillin resistant, and 1 did not have available sensitivity data. Of the 21 patients with methicillin-resistant isolates, 17 had received cefazolin alone for surgical prophylaxis, 2 had received vancomycin, 1 had received levofloxacin, and 1 did not have available surgical prophylaxis data. There was no standard procedure regarding preoperative screening for *S. aureus* colonization. Of the coagulase-negative staphylococcal isolates, 6 were methicillin susceptible, 14 were methicillin resistant, and 14 did not have available sensitivity data. Of the 14 patients with methicillin-resistant isolates, 12 received cefazolin alone for surgical prophylaxis, 1 received

Table 2. Depression History Among Study Patients

Depression History Variable	Patients, No. (%)[a] All patients (n = 387)	Case Patients (n = 129)	Controls (n = 258)	*P* Value
Recorded diagnosis of depression	33 (8.55)	12 (9.4)	21 (8.14)	.70
Abnormal preoperative mood[b]	19 (6.4)	13 (13.0)	6 (3.1)	.005
"Depressed" preoperative mood	7 (2.3)	6 (6.0)	1 (0.5)	.03
Preoperative *ICD-9* code for depression	15 (3.9)	5 (3.9)	10 (3.9)	>.99
Taking antidepressant[c]				
At time of surgery	45 (11.7)	21 (16.3)	24 (9.4)	.05
Within 1 y of surgery	49 (12.7)	23 (17.8)	26 (10.2)	.03
Depression history[d]	57 (14.7)	28 (21.7)	29 (11.2)	.01

Abbreviation: *ICD-9, International Classification of Diseases, Ninth Revision*.

[a]Some data were missing; 90 patients lacked documentation of their mood on the preoperative review of systems, 3 lacked documentation of a home medication list at time of surgery, and 280 patients did not have an additional medication list from within 1 year before surgery.

[b]Mood recorded as anything other than "normal" on the preoperative review of systems.

[c]Either a first-line antidepressant (bupropion, selective serotonin reuptake inhibitor, or serotonin-norepinephrine reuptake inhibitor) or >1 antidepressant.

[d]Depression history was defined as having a recorded diagnosis of depression in the medical record, a depressed mood on preoperative review of systems, a preoperative *ICD-9* code for depression, or a history of antidepressant use at the time of surgery or in the year before surgery.

vancomycin and gentamicin, and 1 did not have available surgical prophylaxis data. Of the 21 *Klebsiella* isolates, 15 were sensitive to cefazolin, 5 were not, and 1 did not have available sensitivity data.

DISCUSSION

A preoperative history of depression, as defined by our composite variable, seems to be associated with a significantly increased risk of SWI after sternotomy or thoracotomy for cardiothoracic surgery, compared with no history of depression. This association remained significant after adjustment for all other significant risk factors. To our knowledge, this is the first study that identifies preoperative history of depression as an independent risk factor for SWI after CABG, valve surgery, coronary artery unroofing, or aortic root surgery. These results will be discussed below in the context of existing literature, possible next steps in research, and clinical implications.

Our results complement existing data that suggest a link between depression and postoperative infection. For example, depression is an independent risk factor for the development of periprosthetic joint infection in patients undergoing total knee arthroplasty and total hip arthroplasty [27, 28]. Our results are also consistent with previous studies addressing outcomes specifically in cardiothoracic surgery. Scheier et al [29] assessed rates of rehospitalization after CABG and found that depression was associated with increased risk of rehospitalization for SWI, and Doering et al [30] found that CABG patients with postoperative depressive symptoms were more likely than patients without such symptoms to have a wound complication (including SWI, saphenous vein harvest site infection, or evidence of impaired wound healing). Our study corroborates and expands on these findings.

In the univariate analysis, antidepressant use was also significantly associated with SWI ($P = .03$). We considered antidepressant use to be a marker of depression history. Of note, though 7 patients were taking bupropion, 5 were not smokers,

Table 3. Baseline Laboratory Values

Laboratory Value	Median (IQR)[a] Case Patients (n = 129)	Controls (n = 258)	*P* Value
Body mass index, kg/m^2	29.6 (9.6)	27.3 (7.7)	<.001
WBC count, WBCs/μL	7.9 (2.6)	7.45 (2.8)	.09
Creatinine, mg/dL	1.1 (0.46)	1.0 (0.3)	.17
GFR, mL/min/1.73 m^2	61.5 (28.6)	66 (28.5)	.07
Albumin, g/dL	3.8 (0.70)	3.9 (0.80)	.98
Total bilirubin, mg/dL	0.6 (0.35)	0.6 (0.30)	.56
Preoperative glucose, mg/dL	125.0 (75.0)	114.0 (47.0)	.10
Postoperative glucose, mg/dL	164.0 (49.5)	151.0 (47.0)	.02

Abbreviations: GFR, glomerular filtration rate; IQR, interquartile range; WBC, white blood cell.

[b]Laboratory values are based on the last recorded value before surgery. Glucose values are only included if recorded within 24 hours of surgery; other values were collected ≤30 days before surgery. Data were missing for body mass index in 7 patients, WBC count in 1, creatinine and GFR in 2, albumin and total bilirubin in 148, preoperative glucose in 142, and postoperative glucose in 2.

Table 4. Intraoperative Variables

Variable	Patients, No. (%)[a]		*P* Value
	Case Patients (n = 129)	Controls (n = 258)	
CABG	90 (70)	131 (50.8)	<.001
Valve and/or aortic root surgery	69 (53.5)	179 (69.4)	.003
Use of BIMA	39 (54.9)	32 (45.1)	.001
Use of prosthetic material	76 (58.9)	153 (70.2)	.01
Urgency of surgery			
Emergent	4 (3.5)	5 (2.4)	.28
Emergent or urgent	31 (27.2)	44 (21.4)	.27
Prophylaxis			
Cefazolin[b]	106 (84.1)	204 (80.3)	.34
Vancomycin	14 (11.1)	27 (10.7)	.81
Vancomycin and gentamicin	6 (4.8)	25 (10.0)	.03
Use of intra-aortic balloon pump	8 (6.2)	7 (2.7)	.10
Use of cardiopulmonary bypass	117 (90.7)	236 (91.5)	.78
Cardiopulmonary bypass duration, mean (SD), min	114.8 (59.5)	114.6 (54.1)	.86

Abbreviations: BIMA, bilateral internal mammary artery. CABG, coronary artery bypass grafting; SD, standard deviation.

[a]Data represent No. (%) of patients unless otherwise specified. Data were missing for urgency of surgery in 67 patients, for antibiotic prophylaxis selection in 7, and for cardiopulmonary bypass duration in 1.

[b]One case patient received both cefazolin and vancomycin and is included in both groups, 2 controls received both cefazolin and vancomycin-gentamicin and are included in both groups, and 1 case patient received prophylaxis with levofloxacin.

Table 5. Multivariable Analysis

Variable	aOR (95% CI)	*P*
Depression history[a]	2.4 (1.2–4.7)	.01
Heart failure	1.7 (1.0–2.7)	.04
Obesity	1.8 (1.1–3.0)	.02
Coronary artery bypass grafting	2.7 (1.6–4.5)	.001
Intra-aortic balloon pump use	4.3 (1.2–14.6)	.02
Age	0.98 (1.0–1.0)	.02
Sex	0.89 (.5–1.5)	.67

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

[a]As defined by the composite definition of depression history (a recorded diagnosis of depression in the medical record, a "depressed" mood on preoperative review of systems, a preoperative *International Classification of Diseases, Ninth Revision,* code for depression, or a history of first-line or combination antidepressant use at the time of surgery or in the year before surgery).

and only 1 patient was taking it for an unknown indication. We therefore considered it unlikely that bupropion use biased the study results. Although many patients do not respond to pharmacotherapy for depression, other effective treatments are available. A randomized controlled trial of an interactive, computerized cognitive behavioral therapy program (Beating the Blues) demonstrated a substantial, statistically significant, and enduring reduction in symptoms of depression [31, 32]. It is likely that reducing the risk of SWI may require both identifying depression and ensuring adequate treatment.

Our results suggest that screening tools can help identify patients at risk for infection. In our univariate analysis, among measures of depression history, an "abnormal" or depressed mood on the preoperative review of systems was associated with the strongest unadjusted risk of SWI ($P = .005$ and $P = .03$, respectively). Among 7 patients who reported a depressed mood, infection developed in 6. A depressed preoperative mood may therefore be a particularly strong signal regarding the risk of postoperative SWI, and the relationship between timing of surgery and severity of mood symptoms is important to investigate further. However, the low number of reviews of systems with reported depressed mood suggests that this measure had poor sensitivity for detecting depression. Validated, sensitive depression screens exist; future studies using standard screening and diagnostic measures to detect depression are warranted.

Our results supported our primary hypothesis that preoperative depression history, as defined by our composite variable, was associated with an increased risk of SWI. Moreover, our findings with regard to the relationship between obesity, heart failure, and intra-aortic balloon pump use and increased risk of SWI are consistent with those of previous studies, which supports the validity of our data [6–8, 13, 33].

Because this was a retrospective study, a limitation is that we did not have a structured psychiatric interview with a set of validated criteria to identify depression. Our composite definition relied on the willingness of the patient to disclose a psychiatric history and the diligence of the interviewer in taking a history, completing the review of systems, and performing an up-to-date medication reconciliation. Although our composite definition has not been validated, other studies have used similar components when assessing for history of depression [34–36]. The aim of the composite definition was to avoid underdetection of depression history. To meet this aim, we sacrificed some specificity of the measure. Even so, in our study, the prevalence of depression was still lower than has been found in previous

studies of patients undergoing cardiothoracic surgery. Because the same measures of detection were used for all patients, depression history was probably equally underdetected in case patients and controls. Although there were missing data (ie, preoperative mood), the proportion of missing data was the same in case patients and controls.

Another limitation of our study may be underdetection of superficial SWI after discharge, as suggested by the high percentage of organ/space infections. Because our hospital is a referral center, many patients do not live close by. Superficial infections that did not require reoperation may have been treated at an outside, local hospital without communication with our surgical team or hospital epidemiologist. We performed a sensitivity analysis to address this issue: when we removed superficial SWI as part of the outcome measure (keeping only deep and organ/space SWIs), the model did not significantly change.

Our study does not shed light on the mechanisms by which depression may increase the risk of SWI, and this requires further investigation. However, a link between depression and infection is biologically plausible. Negative mood symptoms, such as stress, are strongly associated with poor wound healing and increased susceptibility to bacterial wound infection in both mice and humans [37–40]. Depression is associated with alterations in immune gene expression regulated by the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary axis with subsequent effects on inflammation and susceptibility to infection [41–44]. There is also an emerging literature on the relationship between the gut microbiome and depression [45]; patients with depression have altered fecal microbiota [46], and some antidepressant medications are thought to have antimicrobial effects that could correct this dysbiosis [47]. Microbiome changes as a result of depression or its treatment could influence pathogen carriage and may mediate subsequent risk of infection.

Identifying risk factors for SWI that are potentially modifiable is the first step toward reducing the risk of infection. Though our study had notable limitations, our identification of a new and significant risk factor for SWI is grounded in a body of literature that has established a link between depression and poor outcomes after cardiothoracic surgery. Our data suggest that preoperative patients should be screened rigorously for depression. Future, prospective studies should further explore this association, parse out which aspect of depression history (preoperative mood, treatment, microbiome changes, neurohormonal pathway changes, etc) may be most correlated with SWI risk, and investigate whether effective interventions for depression could decrease the risk of SWI.

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References

1. Cristofolini M, Worlitzsch D, Wienke A, et al. Surgical site infections after coronary artery bypass graft surgery: incidence, perioperative hospital stay, readmissions, and revision surgeries. Infection **2012**; 40:397–404.
2. Paul M, Raz A, Leibovici L, et al. Sternal wound infection after coronary artery bypass graft surgery: validation of existing risk scores. J Thorac Cardiovasc Surg **2007**; 133:397–403.
3. Hollenbeak CS, Murphy DM, Koenig S, et al. The clinical and economic impact of deep chest surgical site infections following coronary artery bypass graft surgery. Chest **2000**; 118:397–402.
4. Filsoufi F, Castillo JG, Rahmanian PB, et al. Epidemiology of deep sternal wound infection in cardiac surgery. J Cardiothorac Vasc Anesth **2009**; 23:488–94.
5. Taylor AH, Mitchell AE, Mitchell IM. A 15-year study of the changing demographics and infection risk in a new UK cardiac surgery unit. Interact Cardiovasc Thorac Surg **2012**; 15:390–4.
6. Ridderstolpe L, Gill H, Granfeldt H, et al. Superficial and deep sternal wound complications: incidence, risk factors and mortality. Eur J Cardiothorac Surg **2001**; 20:1168–75.
7. Olsen MA, Lock-Buckley P, Hopkins D, et al. The risk factors for deep and superficial chest surgical-site infections after coronary artery bypass graft surgery are different. J Thorac Cardiovasc Surg **2002**; 124:136–45.
8. Crabtree TD, Codd JE, Fraser VJ, et al. Multivariate analysis of risk factors for deep and superficial sternal infection after coronary artery bypass grafting at a tertiary care medical center. Semin Thorac Cardiovasc Surg **2004**; 16:53–61.
9. Colombier S, Kessler U, Ferrari E, et al. Influence of deep sternal wound infection on long-term survival after cardiac surgery. Med Sci Monit **2013**; 19:668–73.
10. Si D, Rajmokan M, Lakhan P, et al. Surgical site infections following coronary artery bypass graft procedures: 10 years of surveillance data. BMC Infect Dis **2014**; 14:318.
11. Berríos-Torres SI, Mu Y, Edwards JR, et al. Improved risk adjustment in public reporting: coronary artery bypass graft surgical site infections. Infect Control Hosp Epidemiol **2012**; 33:463–9.
12. Vuorisalo S, Haukipuro K, Pokela R, Syrjälä H. Risk features for surgical-site infections in coronary artery bypass surgery. Infect Control Hosp Epidemiol **1998**; 19:240–7.
13. Bryan CS, Yarbrough WM. Preventing deep wound infection after coronary artery bypass grafting: a review. Tex Heart Inst J **2013**; 40:125–39.
14. Fráguas Júnior R, Ramadan ZB, Pereira AN, Wajngarten M. Depression with irritability in patients undergoing coronary artery bypass graft surgery: the cardiologist's role. Gen Hosp Psychiatry **2000**; 22:365–74.
15. Connerney I, Shapiro PA, McLaughlin JS, et al. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. Lancet **2001**; 358:1766–71.
16. Rozanski A, Blumenthal JA, Davidson KW, et al. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol **2005**; 45:637–51.
17. Konstam V, Moser DK, De Jong MJ. Depression and anxiety in heart failure. J Card Fail **2005**; 11:455–63.
18. Frasure-Smith N, Lespérance F, Habra M, et al; Atrial Fibrillation and Congestive Heart Failure Investigators. Elevated depression symptoms predict long-term cardiovascular mortality in patients with atrial fibrillation and heart failure. Circulation **2009**; 120:134–40.
19. Brown JM, Stewart JC, Stump TE, Callahan CM. Risk of coronary heart disease events over 15 years among older adults with depressive symptoms. Am J Geriatr Psychiatry **2011**; 19:721–9.
20. Adams J, Kuchibhatla M, Christopher EJ, et al. Association of depression and survival in patients with chronic heart failure over 12 years. Psychosomatics **2012**; 53:339–46.
21. Rogers MA, Greene MT, Young VB, et al. Depression, antidepressant medications, and risk of *Clostridium difficile* infection. BMC Med **2013**; 11:121.
22. Troidle L, Watnick S, Wuerth DB, et al. Depression and its association with peritonitis in long-term peritoneal dialysis patients. Am J Kidney Dis **2003**; 42:350–4.

23. Adams TB, Wharton CM, Quilter L, Hirsch T. The association between mental health and acute infectious illness among a national sample of 18- to 24-year-old college students. J Am Coll Health **2008**; 56:657–63.
24. Seminog OO, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. Thorax **2013**; 68:171–6.
25. Gordon RJ, Weinberg AD, Pagani FD, et al; Ventricular Assist Device Infection Study Group. Prospective, multicenter study of ventricular assist device infections. Circulation **2013**; 127:691–702.
26. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control **2008**; 36:309–32.
27. Bozic KJ, Lau E, Kurtz S, et al. Patient-related risk factors for postoperative mortality and periprosthetic joint infection in Medicare patients undergoing TKA. Clin Orthop Relat Res **2012**; 470:130–7.
28. Bozic KJ, Ong K, Lau E, et al. Estimating risk in Medicare patients with THA: an electronic risk calculator for periprosthetic joint infection and mortality. Clin Orthop Relat Res **2013**; 471:574–83.
29. Scheier MF, Matthews KA, Owens JF, et al. Optimism and rehospitalization after coronary artery bypass graft surgery. Arch Intern Med **1999**; 159:829–35.
30. Doering LV, Moser DK, Lemankiewicz W, et al. Depression, healing, and recovery from coronary artery bypass surgery. Am J Crit Care **2005**; 14:316–24.
31. Proudfoot J, Goldberg D, Mann A, et al. Computerized, interactive, multimedia cognitive-behavioural program for anxiety and depression in general practice. Psychol Med **2003**; 33:217–27.
32. Proudfoot J, Ryden C, Everitt B, et al. Clinical efficacy of computerised cognitive-behavioral therapy for anxiety and depression in primary care: randomised controlled trial. Br J Psychiatry **2004**;185:46–54.
33. Borger MA, Rao V, Weisel RD, et al. Deep sternal wound infection: risk factors and outcomes. Ann Thorac Surg **1998**;65:1050–56.
34. Stenman M, Holzmann MJ, Sartipy U. Relation of major depression to survival after coronary artery bypass grafting. Am J Cardiol **2014**; 114:698–703.
35. Stenman M, Holzmann MJ, Sartipy U. Do socioeconomic factors modify the association between preoperative antidepressant use and survival following coronary artery bypass surgery? Int J Cardiol **2015**; 198:206–12.
36. Xiong GL, Jiang W, Clare R, et al. Prognosis of patients taking selective serotonin reuptake inhibitors before coronary artery bypass grafting. Am J Cardiol **2006**; 98:42–7.
37. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, et al. Slowing of wound healing by psychological stress. Lancet **1995**; 346:1194–6.
38. Broadbent E, Petrie KJ, Alley PG, Booth RJ. Psychological stress impairs early wound repair following surgery. Psychosom Med **2003**; 65:865–9.
39. Rojas IG, Padgett DA, Sheridan JF, Marucha PT. Stress-induced susceptibility to bacterial infection during cutaneous wound healing. Brain Behav Immun **2002**; 16:74–84.
40. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol **2005**; 5:243–51.
41. Irwin M, Cole S. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol **2011**;11:625–32.
42. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry **2009**; 65:732–41.
43. Kiecolt-Glaser JK, Glaser R. Depression and immune function: central pathways to morbidity and mortality. J Psychosom Res **2002**; 53:873–6.
44. Cole SW, Hawkley LC, Arevalo JM, et al. Social regulation of gene expression in human leukocytes. Genome Biol **2007**;8:R189.181-113.
45. Slyepchenko A, Maes M, Jacka FN, et al. Gut microbiota, bacterial translocation, and interactions with diet: pathophysiological links between major depressive disorder and non-communicable medical comorbidities. Psychother Psychosom **2017**; 86:31–46.
46. Jiang H, Ling Z, Zhang Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun **2015**; 48:186–94.
47. Macedo D, Filho AJMC, Soares de Sousa CN, et al. Antidepressants, antimicrobials or both? gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness. J Affect Disord **2017**; 208:22–32.