ORIGINAL RESEARCH

Outcomes After Prolonged ICU Stays in Postoperative Cardiac Surgery Patients

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Background: Prolonged postoperative intensive care unit (ICU) stays are common after cardiac surgery and are associated with poor outcomes. There are few studies evaluating how risk factors associated with mortality may change during prolonged ICU stays or how mortality may vary with length of stay. We evaluated operative and long-term mortality in post-cardiac surgery patients after prolonged ICU stays at 7, 14, 21, and 28 days and factors associated with mortality.

Methods: We included University of Michigan Medical Center cardiac surgery patients with ≥ 7 postoperative days in the ICU. We determined factors associated with hospital mortality at 7, 14, 21, and 28 days of ICU stay using logistic regression, and among hospital survivors, we determined the factors associated with long-term mortality using Cox regression.

Results: Of 8309 ICU admissions from cardiac surgery, 1174 (14%) had ICU stays > 7 days. Operative mortality was 11%, 18%, 22%, and 35% for the 7-, 14-, 21-, and 28-day groups, respectively. Mechanical ventilation on the day of assessment was associated with increased odds ratios of operative mortality in all models. Of the 1049 (89%) hospital survivors, 420 (40%) died by late follow-up. Median (IQR) Cox model survival was 10.7 (0.7) years. Longer ICU stays, postoperative pneumonia, and elevated discharge blood urea nitrogen were associated with increased hazard of dying; whereas higher discharge platelet count and cardiac transplant were protective.

Conclusions: Both operative and late mortality increased as the duration of a ICU stay increased after cardiac surgery.

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Prolonged intensive care unit (ICU) stays, variably defined as > 48 h to > 14 days, are a known complication of cardiac surgery.[1-8] Prolonged stays are associated with higher resource utilization and higher mortality.[2,3,9-12] Although there are several cardiac surgery risk models that can be used preoperatively to identify patients at risk for prolonged ICU stay, factors that influence outcomes for patients who experience prolonged ICU stays are poorly understood.[2,13-19] Little information is available to inform discussions between health care practitioners (HCPs) and patients throughout a prolonged ICU stay, especially those ≥ 7 days.

As cardiac surgical complexity, patient age, and preexisting comorbidities have increased over time, so has the need to provide patients and HCPs with data to inform decision making, enhance prognostication, and set realistic expectations at varying time intervals during prolonged ICU stay. The purpose of this study was to evaluate short- and long-term outcomes in cardiac surgery patients after prolonged ICU stays at relevant time intervals (7, 14, 21, and 28 days) and to determine factors that may predict a patient's outcome after a prolonged ICU stay.

METHODS

The University of Michigan Health System Institutional Review Board approved this study and waived informed consent. We merged the University of Michigan Medical Center Society of Thoracic Surgeons (STS) database, which is updated periodically with late mortality, with elements of the electronic health record (EHR). Adult patients were included if they had cardiac surgery at the University of Michigan between January 2, 2001, and December 31, 2011. Late mortality was updated through December 1, 2014. Data are presented as frequency (%), mean (SD), and median (IQR) as appropriate. Bivariate comparisons between survivors and nonsurvivors were done with χ^2 or Fisher exact test for categorical data, Student *t* test for continuous normally distributed data, and Wilcoxon rank sum test for continuous not normally distributed data. To determine factors associated with operative mortality (death within 30 days of surgery or hospital discharge, whichever occurred later), we used logistic regression with forward selection. All available factors were initially entered in the models.

Separate logistic models were created based on all data available at days 7, 14, 21, and 28. Final models consisted of factors with statistically significant *P* values (< .05) and adjusted odds ratios (AORs) with 95% CIs that excluded 1. To determine factors associated with late mortality, we used a Cox proportional hazard model, which used data available at discharge and STS complications. As these complications did not include their timing, they could only be used in models created at discharge and not for days 7, 14, 21, and 28 models. Final models consisted of factors with *P* values < .05 and

95% CIs of the AORs or the hazard ratios (HRs) that excluded 1. As the EHR did not start recording data until January 2, 2004, and its capture of data remained incomplete for several years, rather than imputing these missing data or excluding these patients, we chose to create an extra categorical level for each factor to represent missing data. For continuous factors with missing data, we first converted the continuous data to terciles and the missing data became the fourth level.[20,21]

The discrimination of the logistic models were determined by the c-statistic and for the Cox proportional hazards model with the Harrell concordance index (C index). Time trends were assessed with the Cochran-Armitage trend test. $P < .05$ was deemed statistically significant. Statistics were calculated with SPSS versions 21-23 or SAS 9.4.

RESULTS

Of 8309 admissions to the ICU after cardiac surgery, 1174 (14%) had ICU stays ≥ 7 days, 386 (5%) ≥ 14 days, 201 (2%) ≥ 21 days, and 80 (0.9%) ≥ 28 days. The prolonged ICU study population was mostly male, White race, with a mean (SD) age of 62 (14) years. Patients had a variety of comorbidities, most notably 61% had hypertension and half had heart failure. Valve surgery (55%) was the most common procedure (n = 651). Twenty-nine percent required > 1 procedure (eAppendix 1, available at doi:10.12788/fp.0300).

The operative mortality for the entire prolonged ICU stay group was 11%, with progressive increases in mortality as ICU stay increased 18%, 22%, and 35% for the ≥ 14, ≥ 21, and ≥ 28 day groups, respectively (Table 1). Univariate analysis demonstrated that survivors were younger and less likely to have comorbidities. Survivors also were less likely to have had valve surgery, require vasopressors, ventilator support, or renal replacement therapy on day 7 (Table 2). At day 14, survivors were more likely to be male, to have ventricular-assist device surgery, and were less likely to have valve surgery (eAppendix 2, available at doi:10.12788/fp.0300). At day 21, survivors were more likely to have presented with cardiogenic shock or heart failure; however, they were also more likely to receive a ventricular-assist device (eAppendix 3, available at doi:10.12788/fp.0300). Similarly, at day 28 operative survivors were more likely to have received a ventricular assist device (eAppendix 4, available at doi:10.12788/fp.0300).

FIGURE 1 Odds Ratio (95% CI) for Operative Mortality for Patients Receiving Mechanical Ventilation on Day of Analysis

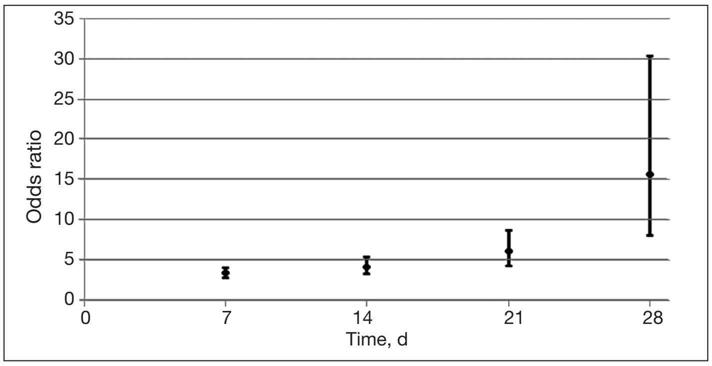
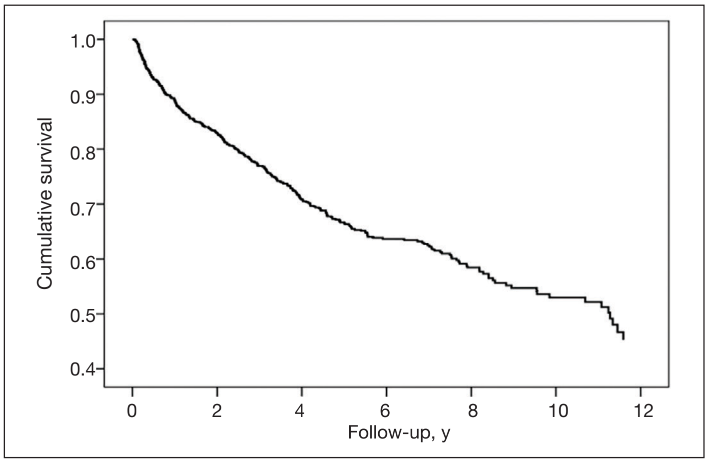
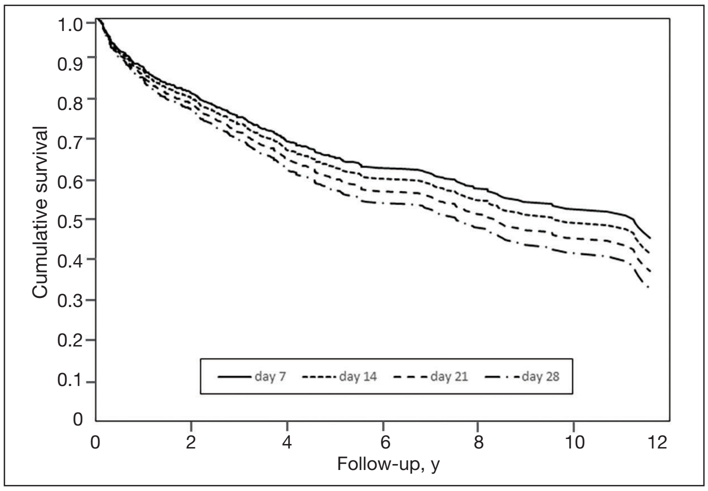


FIGURE 2 Cox Regression for Long-Term Survival in All Patients With Prolonged ICU Surviving to Discharge



Abbreviation: ICU, intensive care unit.

FIGURE 3 Cox Regression for Long-Term Survival in ICU Patients Surviving to Discharge for Prolonged Stays



Abbreviation: ICU, intensive care unit.

TABLE 1 Mortality for Patients With Prolonged ICU Stay After Cardiac Surgery

Length of stay, d	Patients, No.	Operative mortality, No. (%)	Total mortality, No. (%)
≥ 7	1174	125 (11)	420 (36)
≥ 14	386	70 (18)	158 (41)
≥ 21	201	44 (22)	96 (48)
≥ 28	80	28 (35)	41 (51)

Abbreviation: ICU, intensive care unit.

TABLE 2 Univariate Analysis of Significant Preoperative Factors Associated With Mortality for Patients With Intensive Care Unit Stays ≥ 7 Days[a]

	At discharge			At follow-up		
Variables	Survived (n = 1049)	Deceased (n = 125)	*P* value	Survived (n = 754)	Deceased (n = 420)	*P* value
Preoperative						
Smoker, No. (%)				261 (35)	211 (50)	< .001
Diabetes mellitus, No. (%)				190 (25)	141 (34)	.003
Renal failure, No. (%)	268 (26)	44 (35)	.02			
Dialysis, No. (%)	58 (6)	15 (12)	.01			
Hypertension, No. (%)				478 (63)	292 (70)	.04
Infectious endocarditis, No. (%)	88 (9)	19 (15)	.02			
Peripheral vascular disease, No. (%)	120 (11)	23 (18)	.03	73 (10)	70 (17)	.001
Age, mean (SD), y	61 (14)	64 (12)	.02	59 (14)	65 (13)	<.001
Weight, mean (SD), kg,				86 (23)	82 (22)	<.001
Body mass index, mean (SD)				27.8 (7.1)	26.3 (6.7)	<.001
Creatinine, mean (SD), mg/dL				1.46 (1.26)	1.71 (1.58)	.04
Hemoglobin, mean (SD), g/dL				12.0 (2.3)	11.5 (2.2)	.004
Hematocrit, mean (SD), %				35.5 (6.7)	34.1 (6.5)	.01
Operative						
Coronary artery bypass grafting, No. (%)				148 (20)	111 (26)	.008
Valve procedure, No. (%)	566 (54)	85 (68)	.003			
Ventricular-assist device procedure, No. (%)	200 (19)	13 (10)	.02			
Transplant procedure, No. (%)				72 (10)	20 (5)	.003
Perfusion time, mean (SD), min	160 (88)	180 (105)	.046			
Intraoperative cryoprecipitate transfusion, median (IQR)	0 (0-0)	0 (0-0)	.02			
Postoperative day 7						
Vasopressor, No. (%)	99 (16)	27 (33)	< .001			
Ventilator support, No. (%)	234 (22)	60 (48)	< .001			
Renal replacement therapy, No. (%)	65 (6)	19 (15)	.001			
Postoperative pneumonia, No. (%)				118 (18)	117 (29)	< .001
Hematocrit, mean (SD), %	29.9 (4.60	29.8 (4.5)	.91	29.5 (4.4)	30.7 (4.8)	.001
Bilirubin, mean (SD), mg/dL	1.7 (2.5)	4.3 (7.3)	.01			
Alanine transaminase, mean (SD), U/L	125 (4.3)	248 (423)	.03			
White blood cells, mean (SD), 10^3/μL	12.1 (5.0)	16.5 (9.6)	< .001			

[a]Data not available for all variables for all patients; for continuous variables with data missing, available data used from total number of patients for survival at discharge, mortality at discharge, survival at follow-up, mortality at follow-up: age, weight, body mass index (1049, 125, 754, 420, respectively); creatinine, hemoglobin, hematocrit (625, 82, 478, 229, respectively); perfusion time (1006, 118, 724, 400, respectively); day 7 creatinine, sodium, chloride, white blood cells (624, 81, 476, 229, respectively); d 7 hemoglobin (622, 80, 474, 228, respectively), d 7 hematocrit (622, 81, 223, 61, respectively), d 7 bilirubin, alanine transaminase, alkaline phosphatase (481, 64, 376, 169, respectively).

Using multivariable logistic regression to adjust for factors associated with mortality, we found that receiving mechanical ventilation on the day of analysis was associated with increased operative mortality with AOR increasing from 3.35 (95% CI, 2.82-3.98) for day 7, to 4.19 (95% CI, 3.25-5.41) for day 14 , to 6.06 (95% CI, 4.25-8.62) for day 21, to 15.68 (95% CI, 8.11-30.13) for day 28; all *P* values < .001 (Figure 1). Use of vasopressors was associated with an increased operative mortality only for the day 7 group, AOR 2.15 (95% CI, 1.17-2.70), *P* < .001. For days 7, 14, and 28, severe or moderate chronic lung disease was associated with increased AOR of operative mortality: 2.19 (95% CI, 1.52-3.14; *P* < .001) for day 7,2.73 (95% CI, 1.99-3.75; *P* < .001) for day 14, and 37.02 (95% CI, 13.57-100.99;

P < .001) for day 28 (Table 3). Of the 1049 (89%) hospital survivors, 420 (40%) died by late follow-up (Figure 2). Median (IQR) Cox model survival was 10.7 (0.7) years for all hospital survivors; however, long-term survival varied by ICU length of stay (Figure 3). Longer ICU stays were associated with higher late mortality: 36% for ≥ 7 days, 41% for ≥ 14 days, 48% for 21 days, and 51% for ≥ 28 days (*P* < .001). Univariate analysis demonstrated that survivors were less likely to have comorbidities or to be ever smokers. Survivors were younger and less likely to have a coronary artery bypass graft and more likely to have transplant surgery compared with patients who died.

After multivariable Cox regression to adjust for confounders, we found that each postoperative week was associated with a 7% higher hazard of dying (HR, 1.07; 95% CI, 1.07-1.07; *P* < .001). Postoperative pneumonia was also associated with increased hazard of dying (HR, 1.59; 95% CI, 1.27-1.99; *P* < .001), as was elevated blood urea nitrogen. In contrast higher discharge platelet count and cardiac transplant were protective factors (Table 4).

TABLE 3 Multivariate Analyses for Significant Factors Associated With Operative Mortality in Prolonged Intensive Care Unit Stays[a]

Prolonged ICU	Odds ratio (95% CI)	*P* value
Day 7		
Prior stroke	1.41 (1.10-1.80)	.006
Chronic lung disease, mild	0.72 (0.57-0.92)	.009
Chronic lung disease, moderate or severe	2.19 (1.52-3.14)	< .001
Hypothermic circulatory arrest	0.47 (0.36-0.61)	< .001
Vasopressor use	2.15 (1.71-2.70)	< .001
Mechanical ventilation	3.35 (2.82-3.98)	< .001
White blood cell count > 13,100/µL	2.47 (1.92-3.18)	< .001
White blood cell count missing	1.43 (1.11-1.85)	.006
Day 14		
Valve surgery	1.45 (1.09-1.92)	.01
Ventricular-assist device surgery	0.36 (0.24-0.56)	< .001
Prior stroke	1.66 (1.20-2.29)	.002
Chronic lung disease, mild	1.23 (1.04-2.24)	.03
Chronic lung disease, moderate or severe	2.73 (1.99-3.75)	< .001
Mechanical ventilation	4.19 (3.25-5.41)	< .001
Hemoglobin ≥ 9.2 g/dL	0.28 (0.14-0.57)	< .001
Alkaline phosphatase 90-138 U/L	3.57 (2.25-5.66)	< .001
Day 21		
Mechanical ventilation	6.06 (4.25-8.62)	< .001
Sodium > 139 mEq/L	0.21 (0.13-0.36)	< .001
Bilirubin 0.7-1.2 mg/dL	7.29 (3.86-13.76)	< .001
Bilirubin missing	0.50 (0.26-0.97)	.04
Day 28		
Infectious endocarditis	27.85 (9.54-81.33)	< .001
Mechanical ventilation	15.68 (8.11-30.31)	< .001
Sodium 137-139 mEq/L	.004 (0.001-0.02)	< .001
Sodium > 139 mEq/L	0.11 (0.04-0.33)	< .001
Sodium missing	0.07 (0.02-0.27)	< .001
Hemoglobin 9-10.1 g/dL	4.00 (1.21-13.21)	.02
Chronic lung disease, mild	2.72 (1.13-6.56)	.03
Chronic lung disease, moderate or severe	37.02 (13.57-100.99)	< .001

Abbreviation: ICU, intensive care unit.

[a]Logistic regression showing factors associated with operative mortality in patients with ≥ 7 ICU d mortality was 125 of 1174 (11%), c-statistic (SEM) = 0.722 (0.010); ≥ 14 ICU d mortality was 70 of 386 (18%), c-statistic (SEM) = 0.750 (0.014); ≥ 21 ICU d mortality was 44 of 201 (22%), c-statistic (SEM) = 0.742 (0.020); ≥ 28 ICU d, mortality was 28 of 80 (35%), c-statistic (SEM) = 0.889 (0.017).

DISCUSSION

We found that operative mortality increased the longer the patient stayed in the ICU, ranging from 11% for ≥ 7 days to 35% for ≥ 28 days. We further found that in ICU survivors, median (IQR) survival was 10.7 (0.7) years. While previous studies have evaluated prolonged ICU stays, they have been limited by studying limited subpopulations, such as patients who are dependent on dialysis or octogenarians, or used a single cutoff to define prolonged ICU stays, variably defined from > 48 hours to > 14 days.[2-7,9-12,22] Our study is similar to others that used ≥ 2 cutoffs.[1,8] However, our study was novel by providing 4 cutoffs to improve temporal prediction of hospital outcomes. Unlike a study by Ryan and colleagues, which found no increase in mortality with longer stay (43.5% for ≥ 14 days and 45% for ≥ 28 days), our study findings are similar to those of Yu and colleagues (11.1% mortality for prolonged ICU stays of 1 to 2 weeks, 26.6% for 2 to 4 weeks, and 31% for > 4 weeks) and others (8%, 3 to 14 days; 40%, >14 days; 10%, 1 to 2 weeks; 25.7% > 2 weeks) in finding a progressively increased hospital mortality with longer ICU stays.[1,4,5,8] These differences may be related to different ICU populations or to improvements in care since Ryan and colleagues study was conducted.

Fewer studies have evaluated factors associated with mortality in cardiac surgery prolonged ICU stay patients. Our study is similar to other studies that evaluated risk factors by finding associations between a variety of comorbidities and process of care associated with both operative and long-term mortality; however, comparison between these studies is limited by the varying factors analyzed.[1,3,5,6,8,9,11] We found that mechanical ventilation on days 7, 14, 21, and 28 was strongly associated

TABLE 4 Cox Regression Showing Factors Associated With Late Mortality in Patients Who Survived to Hospital Discharge

Factors	Odds ratio (95% CI)	*P* value
Transplant surgery	0.32 (0.19-0.54)	< .001
Smoke	1.34 (1.09-1.66)	.005
Body mass index	1.00 (0.99-1.00)	.002
Chronic lung disease		
Mild	1.39 (1.04-1.85)	.02
Moderate	1.59 (1.10-2.29)	.01
Severe	1.64 (1.05-2.58)	.03
Postoperative pneumonia	1.59 (1.27-1.99)	< .001
Postoperative ICU, length of stay/wk	1.07 (1.07-1.07)	< .001
Discharge day levels		
Alanine transaminase > 57 U/L	0.52 (0.35-0.77)	.001
Urea nitrogen > 35 mg/dL	2.15 (1.50-3.07)	< .001
Chloride 101-104 mmol/L	0.63 (0.49-0.89)	.01
Chloride >104 mmol/L	0.66 (0.48-0.92)	.01
Platelet > 321×103/μL	0.41 (0.28-0.59)	< .001

Abbreviation: ICU, intensive care unit.
[a]Mortality: 420 of 1049 (40%); Harrell c-statistic (SEM) = 0.757 (0.030).

with operative mortality, similar to noncardiac surgery patients and cardiac surgery patients.[6,23,24] While we found several processes of care, such as catecholamine use and transfusions to be associated with mortality, which is similar to other studies, notably, we did not find an association between renal replacement therapy and mortality.[1,25] While there is an association between renal replacement therapy and mortality in ICU patients, its status in cardiac surgery patients with prolonged ICU stays is less clear.[26] While Ryan and colleagues found an association between renal replacement therapy and hospital mortality in patients staying ≥ 14 days, they did not find it in patients staying ≥ 28 days.[1] Other studies of prolonged ICU stays for cardiac surgery patients have also failed to find an association between renal replacement therapy and mortality.[5,6,9] Importantly, practice that expedites liberation from mechanical ventilation, such as fast tracking, daily spontaneous breathing trials, extubation to noninvasive respiratory support, and pulmonary rehabilitation may all have potential to limit mechanical ventilation duration and improve hospital survival and deserve further study.[27-29]

Median (IQR) survival in hospital survivors was 10.7 (0.7) years, which is generally better than previously reported, but similar to that reported by Silberman and colleagues.[2,4,6,8,11,12] Differences between these studies may relate to different patient populations within the cardiac surgery ICUs, definitions of prolonged ICU stays, or eras of care. Further study is needed to clarify these discrepancies. We found that cardiac transplantation and obesity were associated with the least risk of dying, while smoking, lung disease, and postoperative pneumonia were independently associated with increased hazard of dying. The obesity paradox, where obesity is protective, has been previously observed in cardiac surgery patients.[30]

Strengths and Limitations

There are several limitations of this study. This is a single center study, and our patient population and processes of care may differ from other centers, limiting its generalizability. Notably, we do fewer coronary bypass operations and more aortic reconstructions and ventricular assist device insertions than do many other centers. Second, we did not have laboratory values for about one-third of patients (preceded EHR implementation). However, we were able to compensate for this by binning values and including missing data as an extra bin.[20,21]

The main strength of this study is that we were able to combine disparate records to assess a large number of potential factors associated with both operative and long-term mortality. This produced models that had good to very good discrimination. By producing models at 7, 14, 21, and 28 days to predict operative mortality and a model at discharge, it may help to provide objective data to facilitate conversations with patients and their families. However, further studies to externally validate these models should be conducted.

CONCLUSIONS

We found that longer prolonged ICU stays are associated with both operative and late mortality. Receiving mechanical ventilation on days 7, 14, 21, or 28 was strongly associated with operative mortality.

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Disclaimer

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Ethics and consent

This study was approved by the University of Michigan Health System Institutional Review Board (HUM00086820 5/20/2014), which waived informed consent.

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