

Intensive Care Units With Low Versus High Volume of Myocardial Infarction: Clinical Outcomes, Resource Utilization, and Quality Metrics

Joshua M. Stolker, MD; Omar Badawi, PharmD, MPH; John A. Spertus, MD, MPH; Ammar Nasir, MD; Kevin F. Kennedy, MS; Ilene H. Harris, PharmD, PhD; Christine S. Franey, MPH; Van Doren Hsu, PharmD; Gary R. Ripple, MD; Gregory H. Howell, MD, MPH; Vincent M. Lem, MD; Paul S. Chan, MD, MSc

Background—The volume-outcome relationship associated with intensive care unit (ICU) experience with managing acute myocardial infarction (AMI) remains inadequately understood.

Methods and Results—Within a multicenter clinical ICU database, we identified patients with a primary ICU admission diagnosis of AMI between 2008 and 2010 to evaluate whether annual AMI volume of an individual ICU is associated with mortality, length-of-stay, or quality indicators. Patients were categorized into those treated in ICUs with low-annual-AMI volume (≤ 50 th percentile, < 2 AMI patients/month, $n=569$ patients) versus high-annual-AMI volume (≥ 90 th percentile, ≥ 8 AMI patients/month, $n=17\ 553$ patients). Poisson regression and generalized estimating equation with negative binomial regression were used to calculate the relative risk (95% CI) for mortality and length-of-stay, respectively, associated with admission to a low-AMI-volume ICU. When compared with high-AMI-volume, patients admitted to low-AMI-volume ICUs had substantially more medical comorbidities, higher in-hospital mortality (11% versus 4%, $P<0.001$), longer hospitalizations (6.9 ± 7.0 versus 5.0 ± 5.0 days, $P<0.001$), and fewer evidence-based therapies for AMI (reperfusion therapy, antiplatelets, β -blockers, and statins). However, after adjustment for baseline patient characteristics, low-AMI-volume ICU was no longer an independent predictor of in-hospital mortality (relative risk 1.17 [0.87 to 1.56]) or hospital length-of-stay (relative risk 1.01 [0.94 to 1.08]). Similar findings were noted in secondary analyses of ICU mortality and ICU length-of-stay.

Conclusions—Admission to an ICU with lower annual AMI volume is associated with higher in-hospital mortality, longer hospitalization, and lower use of evidence-based therapies for AMI. However, the relationship between low-AMI-volume and outcomes is no longer present after accounting for the higher-risk medical comorbidities and clinical characteristics of patients admitted to these ICUs. (*J Am Heart Assoc.* 2015;4:e001225 doi: 10.1161/JAHA.114.001225)

Key Words: acute myocardial infarction • intensive care unit • outcomes research • quality of care • volume-outcome relationship

Nearly 6 million adults are admitted annually to intensive care units (ICUs) in the United States, and hospital expenditures for ICU patients exceed \$70 billion each year.¹ Given the complexity of contemporary ICU patients, many

hospitals have designated specialty ICUs to improve resource utilization and clinical outcomes when treating patients with primary cardiac, surgical, medical, or neurologic diagnoses.^{2,3} For example, patients with acute myocardial infarction (AMI) admitted to an ICU often require specialized management strategies such as early recognition and treatment of ventricular arrhythmias, unique anticoagulation therapies, and use of intra-aortic balloon pump or ventricular assist devices.⁴ These AMI therapies may require skills, resources, and experience that are not readily available in ICUs with lower annual AMI volume. Although several studies have demonstrated better outcomes among AMI patients treated by *physicians* or *hospitals* with higher patient volume,^{5,6} these volume-outcome relationships have not been explored at the ICU level.

To better understand the relationship between ICU experience and AMI outcomes, we used a multicenter clinical ICU

From Mercy Heart and Vascular, Washington, MO (J.M.S.); Saint Louis University, St Louis, MO (J.M.S., A.N.); Philips Healthcare, Baltimore, MD (O.B.); University of Maryland School of Pharmacy, Baltimore, MD (O.B., C.S.F., V.D.H.); Saint Luke's Mid America Heart and Vascular Institute, Kansas City, MO (J.A.S., K.F.K., P.S.C.); IMPAQ International, Columbia, MD (I.H.H.); Midwest Pulmonary Consultants, Kansas City, MO (G.R.R., G.H.H., V.M.L.).

Correspondence to: Joshua M. Stolker, MD, 901 Patients First Drive, Washington, MO 63090. E-mail: jstolker@yahoo.com

Received July 20, 2014; accepted April 20, 2015.

© 2015 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley Blackwell. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

database to identify and characterize ICUs with low AMI volume (LMIV) and those with high AMI volume (HMIV). We then evaluated whether management of AMI patients in ICUs with LMIV is associated with differences in mortality, length-of-stay, or quality metrics for AMI when compared with patients admitted to ICUs with HMIV.

Methods

Patient Population

The data source for this observational study is the Philips eICU Research Institute (eRI) data repository, a multicenter clinical database of 795 780 patients admitted to 348 ICUs between January 2008 and September 2010. The eICU[®] is a remote ICU monitoring system that provides medical oversight for ICU patients from centralized monitoring centers at >300 hospitals across the United States.⁷

We identified 35 806 adult patients with AMI as the admitting ICU diagnosis within the eRI repository (Figure 1). Only the first ICU admission per patient was included. To avoid confounding from patients who received minimal ICU management prior to death or transfer (eg, to the operating room for bypass surgery, or to another ICU), patients with an ICU length of stay of <2 hours were excluded. We also excluded patients with non-ICU status (ie, overflow from medical floors or “stepdown” units), patients who remained hospitalized at the end of the eRI data collection period in September 2010, and those with missing or invalid Acute

Physiology And Chronic Health Evaluation-Fourth Revision (APACHE-IV[®]) scores.⁸ In order to focus on ICU triage at hospitals with multiple specialty ICUs, hospitals with ≤250 beds were excluded, as these hospitals were expected to have fewer ICUs and more combined units (medical–cardiac ICU, medical–surgical ICU, etc), which could confound the interpretation of ICU triage for AMI patients. After applying these inclusion and exclusion criteria, there were 22 554 unique patient admissions eligible for analysis.

When evaluating annual AMI volume across ICUs, the distribution curve was continuous from the lowest to the highest AMI volume per ICU. As a result, there was no clear cut point for evenly dividing the analytic cohort into ICUs with low versus high AMI volume. Since our goal was to specifically evaluate whether any relationship existed between admission to an ICU with limited AMI experience and differential patient characteristics and outcomes, we elected to sacrifice statistical power to maximize interpretability of the study findings. As such, patients admitted to ICUs with intermediate AMI volume were excluded to provide the best opportunity to compare patients in ICUs with “unequivocal” experience treating AMI versus those ICUs with much more limited AMI experience. We therefore defined ICUs at or below the 50th percentile of annual AMI admissions per year as LMIV-ICUs, and ICUs at ≥90th percentile of annual AMI admission volume as HMIV-ICUs. This translated into HMIV units admitting at least 8 AMI patients per month, and LMIV units admitting fewer than 1.3 AMI patients per month.

Data Definitions

Patient-level medical diagnoses were systematically collected for APACHE-IV scoring by eICU nurses or other staff, according to the standard clinical protocol at each eICU monitoring center. Diagnoses for the present study were derived from the APACHE-IV data,⁹ with study inclusion based on AMI as the primary reason for ICU admission, and other diagnoses drawn directly from the active problem list for each patient. When specific medical comorbidities were not captured by APACHE, these additional diagnoses were obtained from the International Classification of Diseases–Ninth Revision codes at ICU admission. Medications, vital signs, and laboratory studies were obtained directly from the eRI data repository, as previously described.¹⁰ The Acute Physiology Score—a measure of acute illness severity at presentation—also was calculated for each patient.¹¹

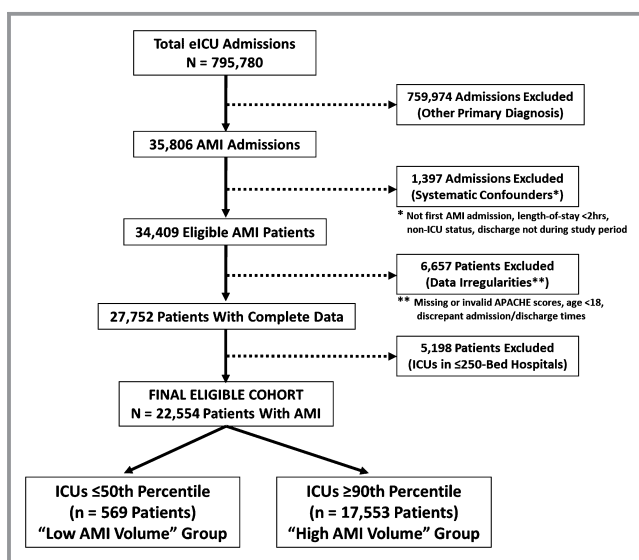


Figure 1. Study flow outlining inclusion and exclusion criteria for ICU patients admitted primarily for AMI. AMI indicates acute myocardial infarction; APACHE, Acute Physiology And Chronic Health Evaluation; eICU, remote ICU monitoring system; ICU, intensive care unit.

Study Outcomes

The primary outcomes for the multivariable analyses were hospital length-of-stay and in-hospital mortality. Secondary outcomes were ICU length-of-stay and ICU mortality. Additionally,

we examined standard quality metrics for patients with AMI (β -blocker use among patients without contraindications, aspirin within the first 24 hours, statin prescription during hospitalization, oral antiplatelet therapy for AMI) and for ICU care in general (prophylaxis against venous thromboembolism among patients at risk, stress ulcer prophylaxis with mechanical ventilation >24 hours) (Table 1).¹² Since the eICU acts as a second level of medical oversight for ICU patients beyond bedside nurses and physicians at individual hospitals, the number of eICU interventions per patient (by remote physicians and by eICU nurses/pharmacists) also was calculated for each patient, as an additional marker of resource utilization.

Statistical Approach

We first compared characteristics of ICUs with LMIV and HMIV using *t* test, χ^2 , and nonparametric alternatives, as appropriate. We then compared patient characteristics and AMI quality indicators of AMI patients admitted to LMIV and HMIV units.

Mortality rates for patients admitted to ICUs with LMIV and HMIV were compared using χ^2 tests. To determine whether admission to an ICU with LMIV was independently associated with higher mortality, modified Poisson regression with robust error variance (to account for clustering within an ICU) was used to estimate the relative risk of death for patients admitted to an ICU with LMIV after adjusting for patient characteristics. This analysis was performed using in-hospital mortality as the primary outcome, but given the potential impact of ICU management on early mortality after admission for AMI, the regression models were rerun using ICU mortality as a secondary outcome of interest.

When evaluating length-of-stay, we used generalized estimating equations with negative binomial regression to compare the overall duration of hospitalization between patients admitted to LMIV and HMIV units, both before and

after adjustment for demographic and clinical characteristics. We then repeated these analyses to assess ICU length-of-stay, as a secondary outcome. The exponentiated coefficients from these models were interpreted as the relative increase or decrease in hospital days or ICU days between the LMIV and HMIV groups.

Candidate variables for the multivariable models were those with nominal significance from bivariate analysis (at $P<0.1$ level) and included demographics (age, sex, race, body-mass index); medical history (diabetes, hypertension, dyslipidemia, tobacco use, peripheral arterial disease, cerebrovascular disease, chronic lung disease, renal dysfunction, metastatic cancer, leukemia or lymphoma, liver failure or cirrhosis, and immune deficiency or suppression); cardiac pathology (prior AMI, ischemic heart disease, and heart failure); presenting ICU diagnoses (ST-elevation AMI, location of AMI, cardiac arrest, heart block, cardiogenic shock, noncardiogenic shock, hypotension, sepsis, pneumonia, pulmonary embolism, respiratory failure, acute renal failure, and gastrointestinal bleeding); hemodynamics (admission and worst mean blood pressure and heart rate within the first 24 hours in the ICU); laboratory studies (admission and worst blood counts, creatinine, glucose, creatine kinase-MB subfraction, and troponin levels); and important medical interventions (percutaneous coronary intervention, thrombolytic therapy, endotracheal intubation, inotropic or vasopressor support, and acute dialysis). As a sensitivity analysis, all multivariable models were repeated after including APACHE-IV score as a covariate. In addition, given the potential for competing predictors of mortality among the candidate variables, the multivariable models were assessed for multicollinearity using the variance inflation factor.¹³

Furthermore, to evaluate whether the differences in outcomes may have been explained by differences among ICU subtype designations, we calculated interaction terms for the comparison of LMIV and HMIV units, and the ICU specialty

Table 1. Best Practice Measures and Adherence Criteria in the eICU[®] Research Institute Database

Best Practice Measure	Inclusion Criteria	Exclusion Criteria	Treatment Criteria
β -Blocker administration*	Acute coronary syndrome diagnosis	Medication allergy, asthma, bronchospasm, bradycardia, hypotension, ophthalmic route of administration	Active order within 24 hours of inclusion criterion documentation, in the absence of contraindications
Venous thromboembolism prophylaxis [†]	ICU length of stay >24 hours	Documented lack of risk such as active ambulation, coagulopathy, already fully anticoagulated	Active order for extremity compression device, anticoagulant medication, or inferior vena cava filter
Stress ulcer prophylaxis	Mechanical ventilation >24 hours	Medication allergy	Active order for proton pump inhibitor, histamine-2 receptor blocker, sucralfate, or antacids

eICU[®] indicates remote ICU monitoring system; ICU, intensive care unit.

*Patients undergoing coronary artery bypass surgery were not included in the at-risk category for β -blocker administration.

[†]Prophylaxis criteria consistent with those endorsed by The Joint Commission and the National Quality Forum (NQF) for ICU patients (NQF #0372).

subtype (ie, cardiac versus noncardiac). ICUs with a cardiac focus were those defined as cardiac ICUs, cardiovascular ICUs, cardiothoracic ICUs, or cardiac surgery ICUs. Noncardiac ICUs were those labeled as medical ICUs, medical-surgical ICUs, neurologic ICUs, surgical ICUs, trauma ICUs, and ventilator ICUs. Specific comparisons also were made between LMIV and HMIV patients admitted to cardiology-specific ICUs, without including the surgical ICUs (ie, only those AMIs managed in cardiac ICUs or cardiovascular ICUs). Lastly, given the significant clinical differences noted between the patient population admitted to LMIV and HMIV units, we performed a propensity match (1:3, meaning 1 LMIV patient matched to 3 HMIV patients) to evaluate mortality and length-of-stay after accounting for these differences between the 2 populations. All baseline clinical characteristics, plus adverse outcomes occurring in the ICU, were used to perform this confirmatory match analysis.

Given the structure of this retrospective analysis of de-identified clinical data, the security schema for the eRI was certified as meeting safe harbor standards by Privacert, Inc (Pittsburgh, PA). The study protocol was deemed exempt by the Institutional Review Board of the University of Maryland School of Medicine under 45 CFR 46.101(b). All authors have reviewed these data and agree to the manuscript as written.

Results

ICU and Patient Characteristics

The final analytic cohort consisted of 569 patients treated in 81 ICUs that had LMIV and 17 553 patients from 41 ICUs that were HMIV units (Figure 1). Most ICUs in our analysis were located at nonteaching hospitals, but hospital size and teaching hospital status were not significantly different between the ICUs with LMIV and HMIV (Table 2). ICUs with LMIV were more commonly designated as medical, surgical, neurological, or mixed ICUs. In contrast, ICUs with HMIV were more likely to be labeled as coronary or cardiovascular surgical ICUs. The 10 most common admission diagnoses for the LMIV group encompassed a variety of surgical, medical, and neurologic diagnoses, whereas admission ICU diagnoses for patients in the HMIV group were almost exclusively cardiac (Table 3).

Patients admitted to ICUs with LMIV were older, more likely to be female, and more likely to have atherosclerotic risk factors and established cardiovascular disease than patients admitted to ICUs with HMIV (Table 4). These individuals also were more likely to have non-Q-wave AMI, other comorbid illnesses in addition to the primary admission diagnosis of AMI, and worse vital signs and laboratory studies plus higher rates of endotracheal intubation and inotropic or pressor support. However, peak troponin levels were lower in the LMIV group, and both medical and coronary reperfusion

Table 2. Characteristics of ICUs With LMIV and HMIV

Characteristic	LMIV (n=81)	HMIV (n=41)	P Value
Hospital size (beds)			0.27
251 to 500	31 (38%)	20 (49%)	
>500	50 (62%)	21 (51%)	
Hospital type			0.30
Teaching	25 (31%)	9 (22%)	
Nonteaching	56 (69%)	32 (78%)	
ICU type			<0.001
Coronary care	5 (6%)	18 (44%)	
Cardiovascular surgical	2 (2%)	11 (27%)	
Mixed	38 (47%)	11 (27%)	
Medical	8 (10%)	1 (2%)	
Surgical	17 (21%)	0 (0%)	
Neurological	9 (11%)	0 (0%)	
Trauma	2 (2%)	0 (0%)	

HMIV and LMIV indicates high and low annual volume of acute myocardial infarction, respectively; ICU, intensive care unit.

therapies for AMI were universally prescribed at lower frequencies than in the HMIV group (Figure 2). Overall, these findings suggested a significantly higher degree of acute and chronic illness at ICU admission, as reflected by markedly higher APACHE-IV scores (52 ± 24 versus 41 ± 19 , $P<0.001$) and Acute Physiology Score scores (38 ± 22 versus 30 ± 16 , $P<0.001$) among AMI patients admitted to ICUs with LMIV. As an exploratory analysis, we also performed 3-way comparisons of these patient characteristics across the LMIV, intermediate volume, and HMIV units. In general, these data confirmed the graded decrease in overall risk profile when moving from LMIV to HMIV. For example, average patient age decreased, medical comorbidities such as diabetes, cerebrovascular disease, and renal dysfunction decreased, and the use of coronary reperfusion therapies increased while moving from LMIV to intermediate volume to HMIV (data not shown).

Patient Outcomes

Patients with AMI admitted to LMIV units had higher in-hospital mortality than those admitted to HMIV units (11% versus 4%, $P<0.001$) (Figure 3). Hospital length-of-stay was also nearly 2 days longer in these individuals (6.9 ± 7.0 versus 5.0 ± 5.0 days, $P<0.001$). Similar findings were noted for ICU mortality (6% versus 3%, $P<0.001$) and ICU length-of-stay (2.9 ± 3.6 versus 2.3 ± 2.6 days, $P<0.001$).

Other adverse clinical events also occurred more commonly among patients in the LMIV group (Table 5), including both cardiovascular complications (atrial arrhythmias, hypotension,

Table 3. Top 10 Admission Diagnoses for ICUs With Low and High Annual Volume of AMI

81 ICUs With Low AMI Volume (Total Admissions=212 007)*		41 ICUs With High AMI Volume (Total Admissions=133 586)*	
Admission Diagnosis	N (%)	Admission Diagnosis	N (%)
Stroke	8557 (4.0)	Acute myocardial infarction	20 231 (15.1)
Coronary bypass surgery	8064 (3.8)	Unstable angina	8275 (6.2)
Other respiratory (medical)	7248 (3.4)	Congestive heart failure	7482 (5.6)
Intracranial hemorrhage/hematoma	5229 (2.4)	Supraventricular rhythm disturbance	5124 (3.8)
Bacterial pneumonia	4383 (2.1)	Chest pain, unknown origin	5053 (3.8)
Coma/change in level of consciousness	4224 (2.0)	Cardiac arrest	4478 (3.4)
Sepsis, pulmonary	4184 (2.0)	Other respiratory (medical)	3887 (2.9)
Diabetic ketoacidosis	3778 (1.8)	Other cardiovascular (medical)	3657 (2.7)
Gastrointestinal bleeding	3753 (1.8)	Coronary bypass surgery	3520 (2.6)
Congestive heart failure	3749 (1.8)	Conduction defect	3109 (2.3)

AMI indicates acute myocardial infarction; ICU, intensive care unit.

*After excluding patients with missing Acute Physiology and Chronic Health Evaluation—Fourth Revision (APACHE-IV) admission diagnoses.

other acute coronary syndromes) and noncardiovascular events (sepsis, pneumonia, respiratory failure, renal failure, and gastrointestinal bleeding). Fewer patients in the LMIV group were discharged from the ICU to home or hospital floors, with more than 3-fold greater likelihood of being transferred to another ICU than the HMIV patients.

When examining quality metrics, more patients in the LMIV group were at risk for noncardiac ICU complications (eg, venous thromboembolism, stress ulcers), but prophylactic therapies were prescribed at similar or higher rates than the ICUs with HMIV. Of the cardiovascular quality indicators, nearly twice as many patients had contraindications to β -blocker therapy in the LMIV group, yet similar proportions of eligible patients (ie, those without contraindications) were treated with these medications. Among patients with ST-elevation AMI, percutaneous or thrombolytic coronary revascularization was performed less frequently within the first 24 hours of ICU admission in the LMIV patients. Of note, interventions by remote monitoring, by both eICU physicians and other eICU medical personnel, were performed more commonly for AMI patients treated in ICUs with LMIV.

Multivariable Models

When evaluating mortality, the unadjusted likelihood of experiencing in-hospital death (relative risk [RR] 2.80 [2.20 to 3.55]) or ICU death (RR 2.39 [1.73 to 3.31]) was higher for AMI patients treated in an ICU with LMIV, when compared with HMIV patients (Figure 4). However, after adjustment for demographics, medical comorbidities, vital signs, and ICU interventions, admission to an ICU with LMIV was no longer associated with either hospital mortality (adjusted RR 1.17

[0.87 to 1.56]) or ICU mortality (adjusted RR 0.96 [0.66 to 1.41]). Similarly, admission to an ICU with LMIV was associated with longer hospital length-of-stay (RR 1.41 [1.32 to 1.51]) and ICU length-of-stay (RR 1.32 [1.21 to 1.43]) in the initial analyses, but these differences were no longer significant after multivariable adjustment (adjusted RR 1.04 [0.97 to 1.12] for hospital length-of-stay, and adjusted RR 0.89 [0.82 to 1.00] for ICU length-of-stay). Of note, the variance inflation factor on the LMIV variable was 1.48, suggesting that collinearity between LMIV and the other independent variables in the multivariable models was low (usual cutoffs generally <5 or <10 in contemporary statistical literature).

Exploratory Analyses

In the secondary analysis evaluating whether ICU subtypes were related to clinical outcomes, for hospital mortality the interaction *P*-value was 0.18, and for ICU mortality the interaction *P*-value was 0.19. This implies that the effect of being admitted to an ICU with LMIV, in terms of both hospital and ICU mortality, did not depend on the ICU subtype (ie, cardiac versus noncardiac). Comparisons of patient characteristics among the subgroup of patients admitted to cardiology-specific ICUs demonstrated similar findings to the overall study, as AMI patients admitted to cardiology-specific ICUs with lesser AMI experience generally had more severe clinical presentations, lower utilization of evidence-based therapies, and worse in-hospital outcomes (Tables 6 and 7). In-hospital mortality for this subgroup of patients in cardiology-specific ICUs was 8% for those admitted to ICUs with LMIV, versus 4% in the ICUs with HMIV (*P*=0.10). Length-of-

Table 4. Patient Characteristics

Characteristic	LMIV Patients (n=569)	HMIV Patients (n=17 553)	P Value
Demographics			
Age, y	68±14	63±14	<0.001
Female sex, %	41	33	<0.001
White race, %	76	78	0.37
Body-mass index, kg/m ²	31±18	30±11	0.22
Medical history			
Diabetes, %	24	19	0.002
Hypertension, %	23	23	0.95
Dyslipidemia, %	9	13	0.003
Cerebrovascular disease, %	4	1	<0.001
AMI in past 6 months, %	5	3	0.013
Systolic heart failure, %	13	6	<0.001
Chronic kidney disease, %	9	5	<0.001
Chronic lung disease, %	10	6	0.001
AMI location			
Anterior, %	15	21	<0.001
Inferior, %	21	35	<0.001
Non-Q-wave AMI, %	52	32	<0.001
Objective findings at ICU admission			
Mean blood pressure, mm Hg	85±20	88±17	0.004
Heart rate, beats per minute	84±20	78±16	<0.001
White blood cell count, ×1000/μL	12±5	11±5	<0.001
Hemoglobin, g/dL	12±2	13±2	<0.001
Creatinine, mg/dL	1.5±1	1.1±1	<0.001
Glucose, mg/dL	154±73	147±71	0.015
Troponin-I, ng/mL	20±67	36±69	<0.001
Troponin-T, ng/mL	3±6	5±11	0.026
Worst laboratory studies within 72 hours			
Lowest hemoglobin, g/dL	11±2	12±2	<0.001
Highest creatinine, mg/dL	1.7±2	1.3±1	<0.001
Highest glucose, mg/dL	198±93	180±93	<0.001
Peak troponin-I, ng/mL	24±70	45±78	<0.001
Peak troponin-T, ng/mL	4±7	5±11	0.031
Major interventions during first 24 hours			
Thrombolytic therapy, %	18	21	0.027
Percutaneous coronary intervention, %	66	78	<0.001

Continued

Table 4. Continued

Characteristic	LMIV Patients (n=569)	HMIV Patients (n=17 553)	P Value
Endotracheal intubation, %	16	5	<0.001
Inotropic or pressor support, %	9	4	<0.001
APACHE-IV	52±24	41±19	<0.001
APS	38±22	30±16	<0.001

Values are expressed as percentages or mean±standard deviation. AMI indicates acute myocardial infarction; APACHE-IV, Acute Physiology and Chronic Health Evaluation, Fourth Revision; APS, Acute Physiology Score; HMIV and LMIV, high and low annual volume of acute myocardial infarction, respectively; ICU, intensive care unit.

stay also was longer in this exploratory analysis: 9±11 days in the LMIV group, versus 5±5 days in the HMIV group ($P<0.001$). Similar findings were noted when comparing ICU mortality (3% versus 3%, $P=0.73$) and ICU length-of-stay (4±5 days versus 2±3 days ($P<0.001$)) between the LMIV and HMIV groups in cardiology-specific ICUs. As a whole, this subgroup analysis was consistent with findings from the overall study—albeit with fewer statistically significant comparisons due to the low numbers of patients in cardiology-specific LMIV ICUs.

In the confirmatory match analysis, 543 of the 569 patients from the original LMIV group were able to be matched with HMIV patients, using all baseline characteristics from Table 4 and the adverse cardiovascular and noncardiovascular events from Table 5. After propensity matching, there were slight differences in body-mass index (31±18 kg/m² versus 29±10 kg/m², $P=0.037$) and both admission troponin-I values (20±68 ng/mL versus 31±72 ng/mL, $P=0.007$) and peak troponin-I values (24±71 ng/mL versus 41±80 ng/mL, $P<0.001$). None of the other 42 variables were significantly different after the match (all $P>0.05$). Within this matched population, there were no differences between LMIV and HMIV patients in experiencing in-hospital mortality (11% versus 10%, $P=0.78$), ICU mortality (6% versus 7%, $P=0.53$), hospital length-of-stay (6.9±7.0 versus 6.7±7.0 days, $P=0.66$), or ICU length-of-stay (2.9±3.6 versus 3.1±3.8 days, $P=0.23$).

Discussion

In this large clinical database of ICU patients managed with additional remote clinical oversight, we found that most patients with a primary diagnosis of AMI were admitted to ICUs with high annual AMI volume, and only a small proportion of these individuals (<5%) were triaged to ICUs with limited experience in AMI management. However, AMI patients in ICUs with LMIV represented an important minority as they required greater eICU involvement, experienced

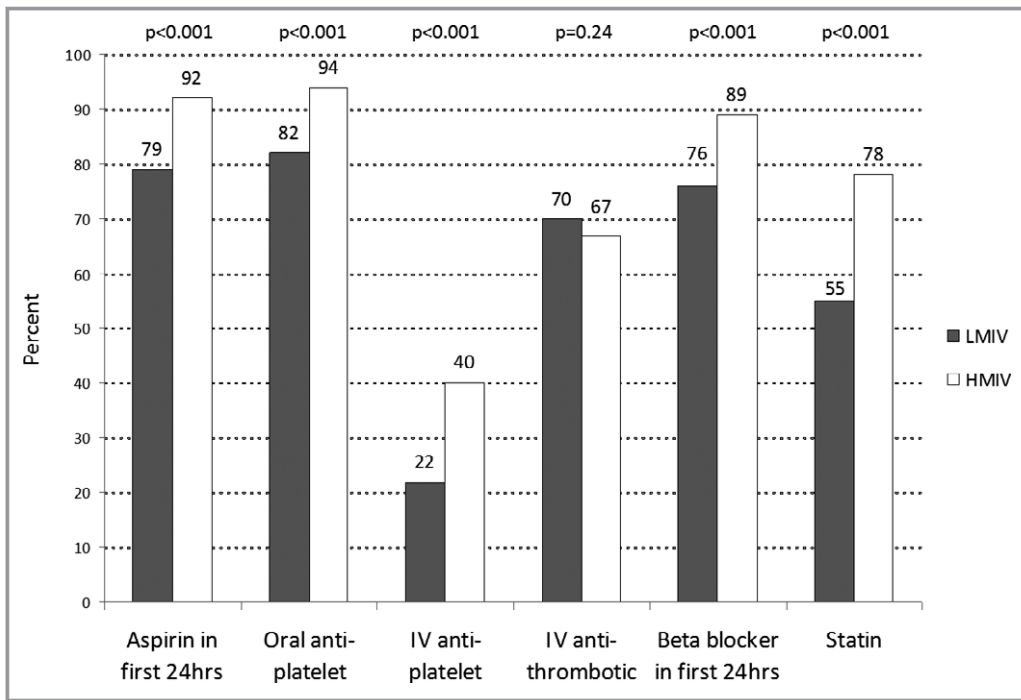


Figure 2. Cardiovascular medications in ICUs with low vs high annual volume of acute myocardial infarction. HMIV and LMIV indicates high and low annual volume of myocardial infarction, respectively; ICU, intensive care unit; IV, intravenous.

longer hospital courses, and were treated less frequently with therapies designated as quality indicators for AMI. Most importantly, these individuals experienced higher rates of

adverse clinical events, including both ICU death and in-hospital death, although these differences were no longer significant after accounting for chronic medical comorbidities

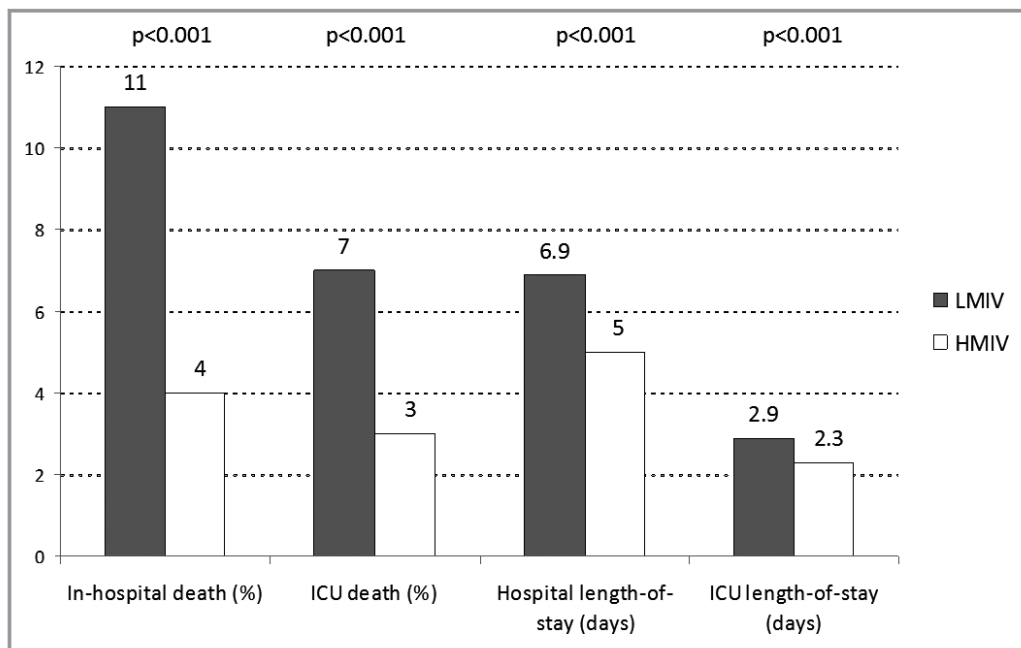


Figure 3. Mortality and length-of-stay among patients admitted to ICUs with low vs high annual volume of acute myocardial infarction. HMIV and LMIV indicates high and low annual volume of myocardial infarction, respectively; ICU, intensive care unit.

Table 5. Clinical Outcomes, Quality Metrics, and Resource Utilization

Event	LMIV Patients (n=569)	HMIV Patients (n=17 553)	P Value
Adverse cardiovascular events in ICU*			
Other acute coronary syndrome, %	5	4	0.06
Cardiac arrest, %	1	2	0.44
Atrial arrhythmia, %	8	4	<0.001
Ventricular arrhythmia, %	2	2	0.41
Cardiogenic shock, %	3	2	0.16
Hypotension, %	8	2	<0.001
Adverse noncardiovascular events*			
Sepsis, %	2	<1	<0.001
Pneumonia, %	5	1	<0.001
Respiratory failure, %	14	4	<0.001
Acute renal failure, %	9	3	<0.001
Gastrointestinal bleeding, %	3	1	<0.001
Disposition from ICU			
Home, %	4	10	<0.001
Hospital floor, %	56	61	0.020
Telemetry floor, %	10	13	0.06
Step-down unit, %	7	6	0.21
Other ICU, %	14	4	<0.001
ICU quality indicators			
At risk for venous thromboembolism, %	53	44	0.06
At risk for venous thromboembolism and receiving prophylaxis, %	96	90	0.012
Ventilated >24 hours at risk for stress ulcers, %	7	2	<0.001
Ventilated >24 hours receiving stress ulcer prophylaxis, %	100	98	1.00
β-Blockers contraindicated despite AMI, %	19	10	<0.001
β-Blockers prescribed among AMI patients without contraindications, %	84	88	0.11
ST-elevation AMI treated with mechanical or thrombolytic revascularization within 24 hours, %	80	89	0.047

Continued

Table 5. Continued

Event	LMIV Patients (n=569)	HMIV Patients (n=17 553)	P Value
eICU[®] resource utilization			
eICU physician interventions per day	1.0±3.6	0.4±1.4	<0.001
eICU non-physician interventions per day	0.1±0.5	0.2±0.7	<0.001

AMI indicates acute myocardial infarction; eICU[®], remote ICU monitoring system; HMIV and LMIV, high and low annual volume of acute myocardial infarction, respectively; ICU, intensive care unit.

*Occurring within 24 hours of ICU admission.

and the acuity of illness at presentation. Similar findings were noted in multiple secondary analyses of ICU subgroups and patient subpopulations. As a result, patients with AMI admitted to ICUs with LMIV appear to represent sicker patients with a greater burden of noncardiac comorbidities, which likely explains both their worse clinical outcomes and their lower use of evidence-based therapies for AMI, when compared with patients in the ICUs with HMIV.

Comparison With Prior Studies

To our knowledge, only 1 study has specifically evaluated the relationship between admission ICU and clinical outcomes after care in a specialty ICU. In an evaluation of ICUs participating in the initial APACHE-IV database between 2002 and 2005, Lott et al found higher mortality rates among the 8% of patients admitted to “non-ideal specialty” ICUs for several different admission diagnoses, including the 6% of patients with AMI admitted to “non-ideal” units.² Our analysis adds to these findings by including patients admitted to unselected ICUs outside of the APACHE-IV study. In addition, specialty ICU designation in the APACHE-IV study was identified by local study coordinators, whereas we avoided ambiguity related to the name of an ICU by specifically identifying ICU categories based on annual AMI volume.

Although our approach may allow for some degree of confounding related to the primary patient subgroup treated in a given ICU (such as the higher rates of coronary artery bypass graft noted in the HMIV group of ICUs), these ICUs would nonetheless have familiarity with AMI management according to AMI volumes (ie, based on the definitions of HMIV and LMIV in this study). Furthermore, this volume-outcome relationship has been demonstrated in multiple prior studies of patients with specific cardiovascular illnesses, as physicians or hospitals with greater experience managing these conditions generally demonstrate better clinical outcomes.^{5,6,14–19} For example, patients treated for heart failure

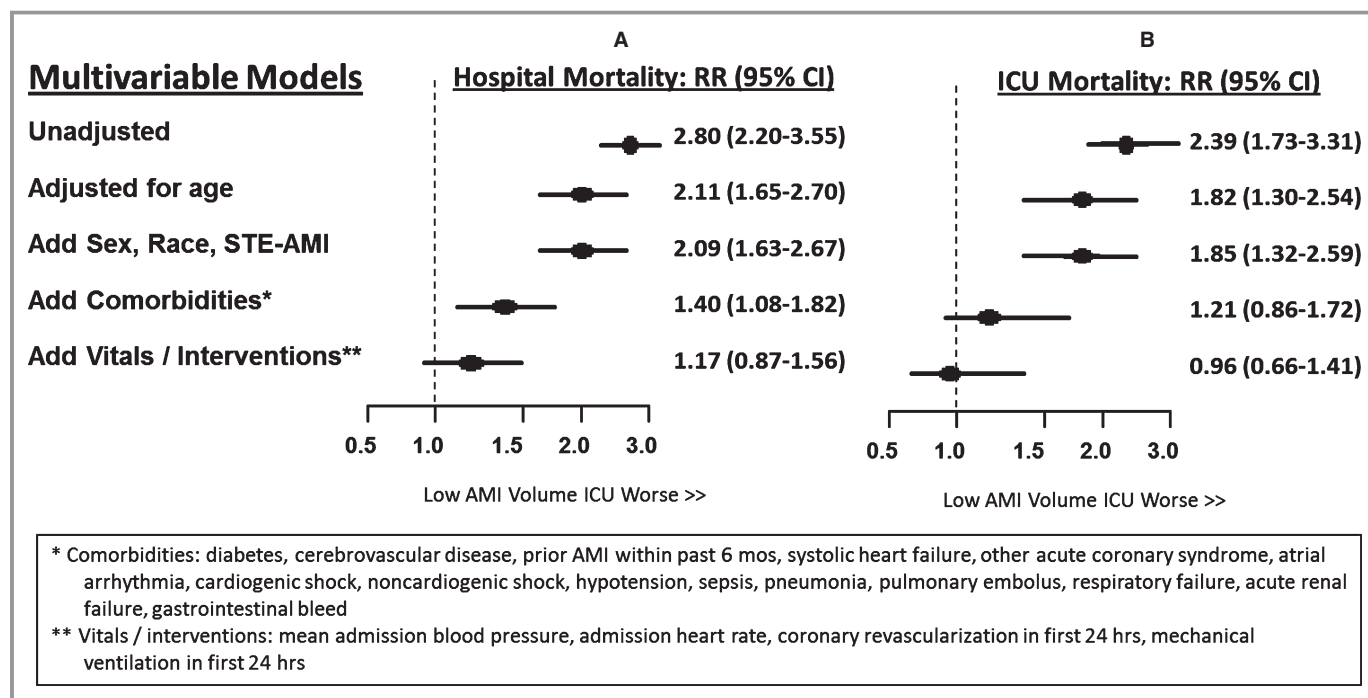


Figure 4. Relationship between admission to an ICU with low annual volume of acute myocardial infarction and (A) in-hospital mortality, or (B) ICU mortality, after adjustment for patient characteristics. AMI indicates acute myocardial infarction; ICU, intensive care unit; RR, relative risk; STE-AMI, ST-segment elevation AMI.

by cardiologists had a reduced risk of readmission within 6 months and overall improved clinical outcomes, when compared with heart failure patients managed by internal medicine or family practitioners.¹⁷ Other studies have demonstrated higher rates of guideline-based therapy and better clinical outcomes among higher-volume hospitals treating AMI.^{5,14,16} Our study extends these findings to AMI patients requiring ICU care, which could provide an opportunity for individual hospitals to carefully evaluate their existing ICU triage systems between specialty units.

Clinical Implications

A key finding in this study is the difference in patient populations between those AMI patients admitted to ICUs with LMIV versus HMIV, as the burden of noncardiac comorbidities among those in the LMIV group likely contributes to the worse clinical outcomes in these individuals. Although multiple prior studies have demonstrated significant variability in ICU triage patterns for patients with differing degrees of acute illness,^{20–23} the relationship between ICU triage and clinical outcomes cannot be reliably evaluated in our study. As a result, it remains unclear whether prospective triage of AMI patients at larger hospitals into a cardiac ICU would affect quality metrics, length-of-stay, or adverse clinical outcomes in these individuals. In addition, the high rates of best-practice metrics in both groups, with minimal difference

in medical therapy between LMIV and HMIV units, likely reflects the oversight by eICU personnel during daily clinical practice, and may have reduced any potential differences in quality metrics and outcomes between the 2 groups of ICUs studied.

Furthermore, while some studies have suggested that local hospital triage measures may improve resource utilization and use of guideline-based therapies,^{2,3,24} the marked difference in patient characteristics in our study instead suggests that a prominent minority of ICU patients require critical care services that cross the boundaries of ICU-subspecialty expertise. Further assessment of ICU triage decisions at the hospital level may help improve local system-based care at some larger hospitals with multiple specialty ICUs, but we believe that a better understanding of cross-collaboration patterns between specialists may be even more important to best serve the most complex of ICU patients.

This issue was raised by a recent scientific statement from the American Heart Association regarding the evolution of critical cardiac care,²⁵ and was echoed by the president of the Society of Critical Care Medicine in 2012.²⁶ In these statements, the authors comment how the management of critically ill cardiac patients has changed dramatically over time, with increasing prevalence of noncardiac comorbidities and noncardiac ICU issues such as mechanical ventilation, sepsis, and multiorgan system failure. As a result, some of the lack of differences in length-of-stay or mortality noted in our

Table 6. Patient Characteristics Among the Subset of Patients Admitted to Cardiology-Specific ICUs

Characteristic	LMIV Patients (n=60)	HMIV Patients (n=12 907)	P Value
Demographics			
Age, y	66±12	63±14	0.09
Female sex, %	37	33	0.56
White race, %	77	81	0.38
Body-mass index, kg/m ²	30±7	30±11	0.97
Medical history			
Diabetes, %	22	19	0.53
Hypertension, %	23	23	1.00
Dyslipidemia, %	18	13	0.19
Cerebrovascular disease, %	2	1	0.46
AMI in past 6 months, %	7	3	0.08
Systolic heart failure, %	18	5	<0.001
Chronic kidney disease, %	7	5	0.43
Chronic lung disease, %	7	6	0.88
AMI location			
Anterior, %	20	21	0.88
Inferior, %	20	33	0.027
Non-Q-wave AMI, %	43	33	0.09
Objective findings at ICU admission			
Mean blood pressure, mm Hg	84±18	88±17	0.045
Heart rate, beats per minute	86±19	78±16	<0.001
White blood cell count, ×1000/μL	12±5	11±4	0.054
Hemoglobin, g/dL	12±2	13±2	0.10
Creatinine, mg/dL	1.3±1	1.1±1	0.11
Glucose, mg/dL	148±67	146±69	0.78
Troponin-I, ng/mL	25±53	35±70	0.52
Troponin-T, ng/mL	3±3	5±11	0.35
Worst laboratory studies within 72 hours			
Lowest hemoglobin, g/dL	11±2	12±2	<0.001
Highest creatinine, mg/dL	1.6±1	1.3±1	0.033
Highest glucose, mg/dL	214±96	178±92	0.003
Peak troponin-I, ng/mL	27±53	44±78	0.33
Peak troponin-T, ng/mL	4±4	6±12	0.38
Major interventions during first 24 hours			
Thrombolytic therapy, %	13	22	0.10
Percutaneous coronary intervention, %	83	75	0.15
Endotracheal intubation, %	28	5	<0.001

Continued

Table 6. Continued

Characteristic	LMIV Patients (n=60)	HMIV Patients (n=12 907)	P Value
Inotropic or pressor support, %	12	5	0.009
APACHE-IV	52±28	41±19	<0.001
APS	40±26	30±17	<0.001

Values are expressed as percentages or mean±standard deviation. AMI indicates acute myocardial infarction; APACHE-IV, Acute Physiology and Chronic Health Evaluation, Fourth Revision; APS, Acute Physiology Score; HMIV and LMIV, high and low annual volume of acute myocardial infarction, respectively; ICU, intensive care unit.

study may stem from the gradual development of systematic oversight from local hospital measures to account for the multiple medical problems affecting contemporary AMI patients. At a simple level, these may include additional cardiology consultations or external oversight from intensivists (or the eICU in our study) providing additional noncardiac care.²⁷ Reducing additional barriers such as obtaining timely ECGs, identifying nurses with greater experience with access-site monitoring after catheterization, or medication titrations performed by cardiology consultants rather than ICU intensivists alone could also impact the care of AMI patients in the ICUs with LMIV.

Study Limitations

Our study findings should be interpreted in the context of several important limitations. In addition to the selection and survival biases inherent to observational studies, the patients in our data set were admitted to ICUs with telemonitoring by eICU nurses and physicians—an extra level of medical oversight previously demonstrated to be associated with improved outcomes and quality metrics.^{27–29} As a result, our findings may not be readily extrapolated to ICUs without remote monitoring. The presence of eICU care may have prevented additional deficiencies in medical care for patients with AMI (as noted by the higher rates of eICU interventions among the LMIV patients), and thus our use of an eICU data set may have attenuated the observed differences in care and outcomes between ICUs with LMIV and HMIV when compared with ICUs without such eICU oversight.

Another important limitation is the inability to identify ICUs within the same hospital, due to privacy concerns related to potential risk of re-identification within the eRI database. This restricted our ability to account for similarities of patients or practice patterns at the hospital level, although we used extensive statistical adjustments to account for latent clustering of patients. Furthermore, the impact of management strategies such as open versus closed ICU care; nurse-to-patient ratio;

Table 7. Clinical Outcomes, Quality Metrics, and Resource Utilization Among the Subset of Patients Admitted to Cardiology-Specific ICUs

Event	LMIV Patients (n=60)	HMIV Patients (n=12 907)	P Value
Adverse cardiovascular events in ICU*			
Other acute coronary syndrome, %	8	4	0.054
Cardiac arrest, %	2	2	0.96
Atrial arrhythmia, %	8	4	0.08
Ventricular arrhythmia, %	3	2	0.49
Cardiogenic shock, %	10	2	<0.001
Hypotension, %	8	2	0.001
Adverse noncardiovascular events*			
Sepsis, %	3	<1	<0.001
Pneumonia, %	0	1	0.39
Respiratory failure, %	18	4	<0.001
Acute renal failure, %	12	3	<0.001
Gastrointestinal bleeding, %	0	1	0.40
Disposition from ICU			
Home, %	3	<1	<0.001
Hospital floor, %	75	66	0.12
Telemetry floor, %	3	9	0.12
Step-down unit, %	3	5	0.65
Other ICU, %	8	5	0.19
ICU quality indicators			
At risk for venous thromboembolism, %	52	43	0.18
At risk for venous thromboembolism and receiving prophylaxis, %	100	89	0.048
Ventilated >24 hours at risk for stress ulcers, %	15	2	<0.001
Ventilated >24 hours receiving stress ulcer prophylaxis, %	100	97	0.61
β-Blockers contraindicated despite AMI, %	26	9	0.002
β-Blockers prescribed among AMI patients without contraindications, %	88	86	0.76
ST-elevation AMI treated with mechanical or thrombolytic revascularization within 24 hours, %	82	88	0.44
eICU [®] resource utilization			
eICU physician interventions per day	0.4±1.4	0.4±1.5	0.86
eICU non-physician interventions per day	0.2±0.6	0.3±0.8	0.49

AMI indicates acute myocardial infarction; eICU[®], remote ICU monitoring system; HMIV and LMIV, high and low annual volume of acute myocardial infarction, respectively; ICU, intensive care unit.

*Occurring within 24 hours of ICU admission.

ICU structure, staffing, and transfer patterns; cardiology consultation rates; overall AMI, interventional, and coronary artery bypass graft volumes per hospital; or physician specialty for a given ICU or patient were not assessed. Any of these important data points may have further influenced AMI outcomes, particularly among the sickest of AMI patients requiring ICU care. Nonetheless, the use of generalized estimating equations for statistical analysis may have helped mitigate some of the differences in hospital-level variability across ICUs, as this approach accounts for the multilevel correlation structure, including clustering on the top-level cluster (ie, hospital site in the present analysis).³⁰ Furthermore, the documentation of admission diagnoses, quality indicators, and medical care was performed by experienced critical care physicians and nurses in an eICU rather than coding specialists with limited medical training, and as a result the fidelity and accuracy of medical variables in the eRI database is likely to be quite high. Although underascertainment of individual patient comorbidities may have occurred while focusing on the critical illnesses prompting ICU admission, there is no a priori reason to expect that such under-reporting would vary according to annual AMI volume of a given ICU, and therefore would be unlikely to affect the overall study findings.

Conclusions

In summary, we found that patients with AMI who are admitted to ICUs with low annual AMI volumes have more extensive acute and chronic medical conditions, and are less likely to receive urgent coronary revascularization or other best-practice measures for AMI. Despite these findings, patients in ICUs with low AMI volume had similar mortality rates and lengths-of-stay when compared with patients in ICUs with high annual AMI volumes, after accounting for the differences in clinical characteristics and comorbidities within this sicker patient population.

Sources of Funding

All analyses from this study were performed externally and independently by the statistical support group at the University of Maryland, using research funding for investigator-initiated studies allocated for this purpose by the eICU Research Institute.

Disclosures

Dr Stolker is a consultant for Cordis and serves on the speakers' bureau for Astra Zeneca, Astellas Pharmaceuticals, and InfraReDx. Dr Badawi is an employee of Philips Healthcare. Dr Harris reports serving as Principal Investigator on a

research contract funded by Philips Healthcare. Dr Spertus reports serving as a consultant to St. Jude Medical, United Healthcare, Amgen, Gilead, Genentech, and Janssen; he also serves as the president of CV Outcomes and Outcomes Instruments, and he receives grant support from Lilly, EvaHeart, Genentech, and Gilead. All other authors have no disclosures to report.

References

- Luce JM, Rubenfeld GD. Can health care costs be reduced by limiting intensive care at the end of life? *Am J Respir Crit Care Med.* 2002;165:750–754.
- Lott JP, Iwashyna TJ, Christie JD, Asch DA, Kramer AA, Kahn JM. Critical illness outcomes in specialty versus general intensive care units. *Am J Respir Crit Care Med.* 2009;179:676–683.
- Angus DC, Shorr AF, White A, Dremsizov TT, Schmitz RJ, Kelley MA. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. *Crit Care Med.* 2006;34:1016–1024.
- Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, Fesmire FM, Ganiats TG, Jneid H, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. *J Am Coll Cardiol.* 2011;57:e215–e367.
- Tu JV, Austin PC, Chan BT. Relationship between annual volume of patients treated by admitting physician and mortality after acute myocardial infarction. *JAMA.* 2001;285:3116–3122.
- Ross JS, Normand SL, Wang Y, Ko DT, Chen J, Drye EE, Keenan PS, Lichtman JH, Bueno H, Schreiner GC, Krumholz HM. Hospital volume and 30-day mortality for three common medical conditions. *N Engl J Med.* 2010;362:1110–1118.
- Celi LA, Hassan E, Marquardt C, Breslow M, Rosenfeld B. The eICU: it's not just telemedicine. *Crit Care Med.* 2001;29:N183–N189.
- Zimmerman JE, Kramer AA, McNair DS, Malila FM, Shaffer VL. Intensive care unit length of stay: benchmarking based on Acute Physiology And Chronic Health Evaluation (APACHE)-IV. *Crit Care Med.* 2006;34:2517–2529.
- Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology And Chronic Health Evaluation (APACHE)-IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med.* 2006;34:1297–1310.
- McShea M, Holl R, Badawi O, Riker RR, Silfen E. The eICU Research Institute—a collaboration between industry, health-care providers, and academia. *IEEE Eng Med Biol Mag.* 2010;29:18–25.
- Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS-II) based on a European/North American multicenter study. *JAMA.* 1993;270:2957–2963.
- Lilly CM, Zuckerman IH, Badawi O, Riker RR. Benchmark data from more than 240,000 adults that reflect the current practice of critical care in the United States. *Chest.* 2011;140:1232–1242.
- Stine RA. Graphical interpretation of variance inflation factors. *Am Stat.* 1995;49:53–56.
- Srinivas VS, Hailpern SM, Koss E, Monrad ES, Alderman MH. Effect of physician volume on the relationship between hospital volume and mortality during primary angioplasty. *J Am Coll Cardiol.* 2009;53:574–579.
- Hannan EL, Wu C, Walford G, King SB III, Holmes DR Jr, Ambrose JA, Sharma S, Katz S, Clark LT, Jones RH. Volume-outcome relationships for percutaneous coronary interventions in the stent era. *Circulation.* 2005;112:1171–1179.
- Roe MT, Chen AY, Mehta RH, Li Y, Brindis RG, Smith SC Jr, Rumsfeld JS, Gibler WB, Ohman EM, Peterson ED. Influence of inpatient service specialty on care processes and outcomes for patients with non ST-segment elevation acute coronary syndromes. *Circulation.* 2007;116:1153–1161.
- Philbin EF, Weil HF, Erb TA, Jenkins PL. Cardiology or primary care for heart failure in the community setting: process of care and clinical outcomes. *Chest.* 1999;116:346–354.
- Freeman JV, Wang Y, Curtis JP, Heidenreich PA, Hlatky MA. The relation between hospital procedure volume and complications of cardioverter-defibrillator implantation from the implantable cardioverter-defibrillator registry. *J Am Coll Cardiol.* 2010;56:1133–1139.
- Al-Khatib SM, Lucas FL, Jollis JG, Malenka DJ, Wennberg DE. The relation between patients' outcomes and the volume of cardioverter-defibrillator implantation procedures performed by physicians treating Medicare beneficiaries. *J Am Coll Cardiol.* 2005;46:1536–1540.
- Chen LM, Render M, Sales A, Kennedy EH, Wiitala W, Hofer TP. Intensive care unit admitting patterns in the Veterans Affairs health care system. *Arch Intern Med.* 2012;172:1220–1226.
- Sprung CL, Geber D, Eidelman LA, Baras M, Pizov R, Nimrod A, Oppenheim A, Epstein L, Cotev S. Evaluation of triage decisions for intensive care admission. *Crit Care Med.* 1999;27:1073–1079.
- Sprung CL, Artigas A, Kesecioglu J, Pezzi A, Wiis J, Pirracchio R, Baras M, Edbrooke DL, Pesenti A, Bakker J, Hargreaves C, Gurman G, Cohen SL, Lippert A, Payen D, Corbella D, Iapichino G. The Eldicus prospective, observational study of triage decision making in European intensive care units. Part II: intensive care benefit for the elderly. *Crit Care Med.* 2012;40:132–138.
- Sinuff T, Kahn moui K, Cook DJ, Luce JM, Levy MM. Rationing critical care beds: a systematic review. *Crit Care Med.* 2004;32:1588–1597.
- Scales DC, Dainty K, Hales B, Pinto R, Fowler RA, Adhikari NK, Zwarenstein M. A multifaceted intervention for quality improvement in a network of intensive care units: a cluster randomized trial. *JAMA.* 2011;305:363–372.
- Morrow DA, Fang JC, Fintel DJ, Granger CB, Katz JN, Kushner FG, Kuvin JT, Lopez-Sendon J, McAreevey D, Nallamothu B, Page RL II, Parrillo JE, Peterson PN, Winkelman C. Evolution of critical care cardiology: transformation of the cardiovascular intensive care unit and the emerging need for new medical staffing and training models: a scientific statement from the American Heart Association. *Circulation.* 2012;126:1408–1428.
- Deutschman CS. Super-subspecialization, fragmentation, competencies, and the practice of critical care medicine. *Crit Connect.* 2012;11:4–5.
- Lilly CM, Cody S, Zhao H, Landry K, Baker SP, McIlwaine J, Chandler MW, Irwin RS. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. *JAMA.* 2011;305:2175–2183.
- Breslow MJ, Rosenfeld BA, Doerfler M, Burke G, Yates G, Stone DJ, Tomaszewicz P, Hochman R, Plocher DW. Effect of a multiple-site intensive care unit telemedicine program on clinical and economic outcomes: an alternative paradigm for intensivist staffing. *Crit Care Med.* 2004;32:31–38.
- Rosenfeld BA, Dorman T, Breslow MJ, Pronovost P, Jenckes M, Zhang N, Anderson G, Rubin H. Intensive care unit telemedicine: alternate paradigm for providing continuous intensivist care. *Crit Care Med.* 2000;28:3925–3931.
- Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol.* 2003;157:364–375.