Incidence of circulatory shock after spontaneous intracerebral hemorrhage and impact on case-fatality: a multi-center cohort study

Lauren Ng, Michelle Ghobrial, James Peoples, Syed Omar Shah, Matthew Vibbert, Jacqueline Urtecho, M. Kamran Athar, Barak Bar, Jack Jallo, Carissa C. Pineda, Diana Tzeng, Rodney Bell, Fred Rincon

Abstract

Objective: The epidemiology of circulatory shock after spontaneous intracerebral hemorrhage (ICH) is unknown. We sought to determine its incidence, risk factors, and effect on case-fatality.

Design: Retrospective multi-center cohort study.

Setting: 83 ICUs in the United States from 2003-2008.

Patients: Subjects with ICH >17 years of age admitted to an ICU. Shock was defined as sustained systolic blood pressure <90 mmHg for ≥1 hour despite vasopressors.

Interventions: None.

Measurements and results: A total of 4,192 ICH patients. Median age was 67 yrs (IQR 54-77), 2221 (53%) were male, and 3030 (75%) were white. Median APACHE-II score was 15 (interquartile-range [IQR] 11-21) and Glasgow Coma Scale (GCS) was 11 (IQR 6-14). Incidence of shock after ICH was 5% (212/4192). Case-fatality was 72% among shock vs. 30% without shock (p<0.0001). In multi-variable analysis the following were associated with increased case-fatality: age (OR 1.01, 95%CI:1.01-1.02), DNR status (OR 1.8, 95%CI:1.3-2.6), GCS<8 (OR 11.4, 95%CI:8.4-15.4), GCS 8-12 (OR 2.1, 95%CI:1.5-2.9), mechanical ventilation (OR 2.0, 95%CI:1.6-2.5), organ dysfunction (OR 1.7, 95%CI:1.4-2.0), spontaneous hypothermia (OR 7.3, 95%CI:2.8-19.3), APACHE ≥15 (OR 2.9, 95%CI:2.2-3.7), and shock (OR 1.9, 95%CI:1.2-3.0). EVD placement was associated with survival (OR 0.8, 95%CI:0.6-0.9).

Conclusion: Circulatory shock after ICH is rare and associated with increased case-fatality.

Key words: Intracerebral hemorrhage, shock, hypotension.

Introduction

Intracerebral hemorrhage (ICH) remains the most devastating type of stroke carrying significant in-hospital mortality (1) and long-term-disability. Upon admission to the Emergency Department (ED) or the Intensive Care Unit (ICU), ICH patients are characteristically hypertensive. (2) Causes of this extreme blood pressure response include: up-regulation of the sympathetic nervous system, renin-angiotensin axis, and pituitary-adrenal axis. (3)

Conversely, hypotension may be rare phenomenon after ICH and usually associated with aggressive pharmacological blood pressure lowering. (2,4,5) In other cases, such as severe volume depletion, cardiac dysfunction, or neurogenic stunned myocardium (NSM), overt circulatory shock may also be seen after ICH. (4,6-10)

No observational study in critically ill ICH patients has been carried-out to assess the occurrence, differential diagnosis, and the risks factors associated with circulatory shock. Based on this paucity of data and limited studies addressing the epidemiology of circulatory shock after ICH, we sought to study the relationship between circulatory shock and case-fatality in a cohort of ICH patients.

Overall, the primary aim of this analysis was to study the epidemiology of circulatory shock after ICH in the ICU using a robust multi-center repository. Specifically, we wanted to determine: a) the occurrence and risk factors of circulatory shock upon admission to the ICU, b) the association between shock and hospital case-fatality, and c)

From Thomas Jefferson University, Philadelphia, PA, USA (Lauren Ng, Michelle Ghobrial, James Peoples, Syed Omar Shah, Matthew Vibbert, Jacqueline Urtecho, M. Kamran Athar, Barak Bar, Jack Jallo, Carissa C. Pineda, Diana Tzeng, Rodney Bell, and Fred Rincon).

Address for correspondence:
Fred Rincon, MD, MSc, MBE
Assistant Professor of Neurology and Neurological Surgery
Department of Neurological Surgery
Thomas Jefferson University and Jefferson College of Medicine
Division of Critical Care and Neurotrauma
909 Walnut Street, 3rd Floor, Philadelphia, PA 19107, USA
Tel: 215-503-7000
Fax: 215-503-7007
Email: fred.rincon@jefferson.edu

whether shock upon admission to the ICU was an early predictor of in-hospital mortality after adjustment for other confounders of poor outcome. We hypothesized that in adults with ICH, shock would not be frequent or associated with higher in-hospital case-fatality.

Methods

Study design and patient population

A retrospective multi-center cohort study utilizing a prospectively compiled and maintained robust registry (Cerner Corporation - Project IMPACT [PI], Bel Air, MD). Our methods have been reviewed elsewhere. (11) Briefly, critically ill patients with a diagnosis of ICH, older than 17 years and consecutively admitted to the ICU from 2003 to 2008 were selected. The following variables were recorded for all patients admitted to the ICU during the study period: emergency department (ED) boarder status, (12) DNR status on admission, demographic variables (age, sex, and race); co-morbidities; clinical variables within 24 hours of admission to ICU: APACHE-II score, Glasgow Coma Score (GCS), vital signs; the need for intracranial pressure monitoring (ICP); and admission and hospital discharge status. (11) The Institutional Review Board of Thomas Jefferson University Hospital (Philadelphia, PA) exempted this analysis from full review.

Definition of main exposure and outcome variables

Shock was defined as a systolic blood pressure ≤90 mmHg for more than 1 hour despite the initiation of a continuous infusion of dopamine, norepinephrine, epinephrine, or phenylephrine, which occurred within the first 24 hours of admission to the ICU. In addition, data from pulmonary artery catheters (PA-C) were also obtained to help with the interpretation of the etiology and differential diagnosis of shock. We recorded: central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), cardiac index (CI), pulmonary artery systolic (PA systolic) pressures, and the left ventricular stroke work index (LVSwi). The primary outcome measure was in-hospital case-fatality. No data on the ICH score, CT scan results, or cardiac ultrasound results were available from the PI repository.

Statistical analyses

Continuous data are presented as means and standard deviations (SD) or medians and interquartile ranges (IQRs) as appropriate based on distribution of the data. Continuous variables were assessed for normality by the Kolmogorov-Smirnov test. Categorical data are reported as proportions and percentages or 95% confidence intervals (CIs). At the univariable level, we compared the exposed groups using the t-test or the Mann-U-Whitney test for continuous variables; and the χ^2 test or the Cochran-Armitage test for trend for categorical variables. For days to primary outcome analysis, Kaplan-Meier survival estimates and log-rank tests were used to compare the exposure groups of interest. In a multivariable analysis, generalized estimating equations (GEE) were used to account for potential correlation in mortality rates among patients sampled within hospital clusters. All variables in **Tables 1** and **2** were considered candidates for the multivariable analysis. We also performed a sensitivity analysis using propensity scores to test if shock remained a significant independent predictor of in-hospital case-fatality. (13,14) We fitted a logistic regression model with shock as the dependent variable and potential candidate variables with p values <0.2 from **Tables 1** and **2**. The results of our logistic regression model were used to calculate each subject's probability of being exposed to shock. The probability (i.e. propensity score) for each subject was then added to our GEE model. Finally, we tested for possible first-order interactions in those variables retained in the model. Statistical analyses were conducted using SPSS software version 20.0 (SPSS Inc., Chicago, Illinois), significance was judged when $p<0.05$. Our reporting of observational data conforms with Strengthening the Reporting of Observational Studies in Epidemiology STROBE guidelines. (15)

Results

There were a total of 4,192 patients from 83 different hospital-based ICUs during the 5 year period. All ICUs were of non-neurological/neurosurgical models. Baseline characteristics of the cohort are shown in **Tables 1** and **2**. There were more males in the cohort, mean age was 69 (IQR 54-77) years, patients were predominantly white (75%) and 3,030 (79%) of the patients were living independently before hospital admission. DNR status upon admission was 8% for the cohort and was not significantly different between exposed groups (**Table 1**).

Upon admission to the ICU, shock was present in 212/4,192 (5%). In the cohort, 0.4% (18/4,192) of patients had a P-AC. The PAOP in patients with shock was 10 mmHg (IQR 5-13) versus 16 mmHg (IQR 8-18) without shock (p=0.049), the CVP was 5 mmHg (IQR 2-11) in shock versus 11 mmHg (IQR 8-15) without shock (p=0.08), the PA systolic were 26 mmHg (IQR 18-30) in shock versus 37

mmHg (IQR 30-47) without shock (p=0.03). Finally, the CI was 3 L/min/m2 (IQR 2.5-3.8) in shock versus 3.8 L/min/m2 (IQR 2.8-4.4) without shock (p=0.3) and the LVSwi was 37 g/m2/beat (IQR 27-41) versus 50 g/m2/beat (45-55) (p=0.03). The hemodynamic characteristics of patients presenting in shock are shown in **Table 2**.

In terms of the primary outcome, the in-hospital case-fatality was 72% of patients who presented with shock as opposed to 30% in those who did not (p<0.0001) (**Table 3**). This is further illustrated in **Figure 1**, which displays the Kaplan-Meyer survival curve for those who shock compared to those without shock. Moreover, ICU and hospital length of stay were less in patients with shock likely due to the increased rates of death (**Table 3**).

In univariable analysis the following were associated with circulatory shock: younger age, fully dependent functional status on admission, DNR upon admission, cardiovascular disease, respiratory disease, admission APACHE-II, lower admission GCS, organ dysfunction, hypothermia, mechanical ventilation, lower pH in ABG, and lower PaO2/FiO2 ratio (**Table 1**). In multivariable analysis, GCS <8 (OR 3.8, 95%CI:2.2-6.9) and organ dysfunction (OR 1.7, 95%CI:1.1-2.4) were associated with shock.

In the final GEE multivariable analysis, which included the probability of developing shock, the following were associated with case-fatality: age (OR 1.01, 95%CI:1.01-1.02), DNR status (OR 1.8, 95%CI:1.3-2.6), GCS<8 (OR 11.4, 95%CI:8.4-15.4), GCS 8-12 (OR 2.1, 95%CI:1.5-2.9), mechanical ventilation (OR 2.0, 95%CI:1.6-2.5), organ dysfunction (OR 1.7, 95%CI:1.4-2.0), hypothermia (OR 7.3, 95%CI:2.8-19.3), APACHE ≥15 (OR 2.9, 95%CI:2.2-3.7), and shock (OR 1.9, 95%CI:1.2-3.0). EVD placement was associated with survival (OR 0.8, 95%CI:0.6-0.9) (**Table 4**). No significant interactions were found.

Discussion

In this large multi-center cohort study of patients presenting with ICH and admitted to the ICU, we have shown that circulatory shock was present in a small proportion of patients, and associated with increased case fatality. Our data suggest that this effect is significant despite the probability of being exposed to circulatory shock (propensity score). Similarly, in those patients with a PA-C, the hemodynamic profile suggested that ICH patients, who developed circulatory shock, had normal CIs; but lower PAOP, PAS, CVP (trend), and LVSwi. This suggests the possibility of systolic dysfunction in the setting of sub-optimal LV filling pressures (pre-load optimization) as the principal etiology of hypotension and shock. Though the number of patients with hemodynamic monitoring was low, our data suggest that in hypotensive ICH patients, recognition, optimization, and targeting of sub-optimal preload related systolic dysfunction should be considered with invasive or non-invasive technologies upon admission to the ICU.

To our knowledge this is the first study that has looked at the incidence and hemodynamic profile of circulatory shock on admission in patients who presented to the ICU with ICH. Though prior studies have shown that low blood pressure level is associated poor outcome and higher case fatality after ICH, (4,5,16-19) the mechanisms and epidemiology of this phenomenon are usually attributed to the temporal association between ICH induced hypertension and pharmacological blood pressure lowering. A small study in a middle-eastern population showed that hypotension, defined as diastolic blood pressure of <70 mmHg, was present in 7% of ICH patients and associated with in-hospital mortality. (4) The etiology or mechanisms related to this observation were not identified or researched by the authors. (4)

In our study, only 5% of the ICH cohort presented with circulatory shock requiring vasoactive medications. Patients with shock on admission to the ICU had significantly higher percentage of cardiovascular comorbidities and cardiac failure (**Table 1**). In support of our data, the study by Putaala et al, which looked at the cardiovascular complications after ICH, found that 4% of these patients had acute systolic heart failure with a total of 4.1% experiencing at least one significant cardiac event. (20) Limited data from our cohort of ICH patients with PA-C, showed a trend towards mild systolic dysfunction, which may have been primarily related to sub-optimal preload as the etiology of circulatory shock. While previous studies showed that the increased mortality was secondary to cardiovascular events, (20) our data suggest that the primary cause of shock in ICH patients may have been systolic dysfunction on the basis of sub-optimal pre-load optimization (i.e. lower PAOP, CVP, PAS and LVSwi). (16,20) This may be supported by the observed relationship between preload, stroke volume, and blood pressure, which is evidenced by a significantly lower LVSwi seen in the shock group. The LVSwi, which is proportional to stroke volume (SV) and mean aortic blood pressure (MAP), is a surrogate of LV contractility and myocardial oxygen consumption. A normal but slightly lower CI in the shock group suggests normal cardiac output in the setting of shock, but

it's important to keep in mind that patients in the shock group were receiving vasoactive medications, which could have potentially optimized the CI, at least transiently. Finally, the lack of difference in urinary output within 24 hours, high temperature, heart rate, respiratory rate, white blood cell counts (i.e. SIRS), and arterial pH makes the possibility of vasodilatory (i.e. septic shock, anaphylaxis); or overt hypovolemic shock or (i.e. hemorrhage) less likely.

The strengths of our study are related to the methodology used to test our hypothesis, the multicenter basis of the cohort ascertainment, and our sensitivity analysis to investigate our internal validity. We also acknowledge the limitations of this study given the observational design and the nature of the database used. First, our analysis is observational in nature, limiting the inferences that can be made about causal relationships. Second, the inherent nature of the database used to perform our analysis, which was designed from an ICU perspective rather than to collect prospective data and endpoints specific to outcome research related to ICH. This suggests the possibility of some residual confounding. Specifically, we were not able to determine the severity of ICH (ICH score or NIHSS), characteristics of ICH or onset of cerebral edema or hematoma volume and growth based on imaging, or pharmacological treatments leading to hypotension. Our multivariable analysis is robust and included classic factors that have been associated with poor outcome in ICH such as age, sex, comorbid conditions, GCS, DNR status, ED boarder status, organ dysfunctions (including coagulopathy), and need for EVD (surrogate of hydrocephalous or ICP), among others. To this end, the advantages of our robust sample size are potentially offset by our inability to audit these important data elements. Third, our analysis may have been subjected to selection bias in the sense that our sample may not be representative of the whole population of ICH or ICUs in the United States. Specifically, we included ICH patients admitted to the ICU. However, the overall in-hospital case-fatality for the whole cohort is in agreement with recent reports and trends of ICH in-hospital mortality in the United States (1) suggesting that we may have included a homogenous sample of ICH patients judging by the distribution of GCS scores (**Table 1**). Finally, because the study focuses on non-neurological/neurosurgical ICUs in the United States, our results may not be generalizable to other settings where management of ICH patients and patient characteristics may differ substantively.

In summary, circulatory shock after ICH is rare but associated with increased case-fatality. Given that PA-Cs are no longer widely used, other hemodynamic monitoring options, such as bedside ultrasonography, aimed at recognizing potentially correctable causes of hypotension may be easily applied in this setting.

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Dr. Rincon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures and conflicts of interest

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Table 1. Patient demographics

Variables	All (n=4192)	Sustained hypotension[c](n=212)	No hypotension (n=3980)	p value
Age, Median (IQR)	67 (54-77)	64 (51-75)	67 (54-77)	0.03
Gender, male n (%)	2221 (53)	103 (49)	2118 (53)	0.2
Race, n (%) n=4061				0.8
• White/caucasian	3030 (75)	150 (75)	2880 (75)	
• Black/African-American	749 (18)	35 (18)	714 (18)	
• Latino/Hispanic	160 (4)	10 (5)	150 (4)	
• Asian/Pacific islander	94 (2)	5 (3)	89 (2)	
• Other	11 (0.2)	0 (0)	11 (0.2)	
Pre-admit functional status, n (%)[a]				0.2*
• Independent	3251 (79)	158 (78)	3093 (79)	
• Partially dependent	580 (14)	24 (12)	556 (14)	
• Fully dependent	281 (7)	21 (10)	260 (7)	
DNR upon admission	348 (8)	25 (12)	323 (8)	0.08
ED boarder	168 (4)	6 (3)	162 (4)	0.3
Co-morbidities[b]				
• Cirrhosis	43 (1)	3 (1)	40 (1)	0.6
• Cardiovascular disease	150 (4)	17 (8)	133 (3)	0.002
• Respiratory disease	74 (2)	9 (4)	65 (2)	0.02
• End stage renal disease	93 (3)	5 (3)	88 (2)	0.9
• HIV status	15 (0.3)	2 (1)	13 (0.3)	0.2
• Cancer	95 (2)	6 (3)	89 (2)	0.6
• Chronic renal failure	165 (4)	8 (4)	157 (4)	0.9
• Chronic steroid use	35 (1)	3 (1)	32 (1)	0.4
• Chemotherapy	109 (3)	9 (4)	100 (3)	0.2
Site of origin before ICU arrival				0.2
• ED	2540 (61)	130 (61)	2410 (61)	
• OSH-ED	741 (18)	46 (22)	695 (17)	
• Inpatient	606 (14)	22 (10)	584 (15)	
• Transfer from other facility	277 (7)	14 (7)	263 (7)	
Admission severity index				
• APACHE-II	15 (11-21)	24 (15-29)	14 (11-21)	<0.0001
GCS				<0.0001*
• GCS <8	1534 (37)	165 (78)	1369 (34)	
• GCS 8-12	784 (19)	15 (7)	769 (19)	
• GCS >12	1874 (45)	32 (15)	1842 (46)	
• GCS median (IQR)	11 (6-14)	3 (3-7)	12 (6-14)	<0.0001
EVD, n (%)	627 (15)	36 (17)	591 (15)	0.4

Organ dysfunction, n (%)[c]				
• Any organ dysfunction	1039 (25)	111 (52)	928 (23)	<0.0001
• Metabolic (lactic acidosis)	47 (1)	7 (3)	40 (1)	0.01
• Respiratory	439 (10)	42 (19)	397 (10)	<0.0001
• Renal	163 (13)	13 (6)	150 (4)	0.11
• Hematologic	172 (4)	10 (5)	162 (4)	0.7
• Hepatic	58 (1)	2 (<1)	56 (1)	0.6
• Neurologic	122 (3)	16 (8)	106 (3)	<0.0001

Legend: DNR=do not resuscitate; ED=emergency department; HIV=human immunodeficiency virus; ICU=intensive care unit; OSH-ED=outside hospital emergency department; APACHE-II=acute physiologic and chronic health assessment score; GCS=Glasgow Coma Scale; EVD=external ventricular drain; *=trend test.

[a] defined as independent (the patient is living at home requiring no assistance in completing activities of daily living, which includes people who are homeless, or who are incarcerated, but otherwise physically and mentally functional); partially dependent (the patient is living at home, in a group home or in a care facility and requires some assistance in completing the activities of daily living and the limitation(s) requiring assistance may be physical or mental); and fully dependent (the patient is living at home or in a care facility and is unable to perform the activities of daily living; must be cared for by other(s); the limitations requiring assistance may be physical or mental).

[b] co-morbidities: cardiovascular disease (defined as baseline symptoms such as angina or shortness of breath at rest or on minimal exertion, NYHA class IV, plus one or more of the following diagnoses: severe coronary artery disease, severe valvular heart or severe cardiomyopathy), respiratory disease (defined as chronic obstructive, restrictive, or vascular pulmonary disease resulting in severe exercise restriction, such as unable to climb stairs or perform household duties; or respirator dependency related to active respiratory disease; or documented chronic hypoxia, hypercapnia, or pulmonary hypertension >40 mmHg), cirrhosis, chronic renal disease or end-stage renal disease, human immunodeficiency virus (HIV) status, and cancer.

[c] organ dysfunction in ICU: sustained hypotension (systolic blood pressure [SBP] <90 mmHg, or MAP <70 mmHg, or vasopressor requirement to keep SBP >90 mmHg or MAP >70 mmHg, and duration >1 hr), metabolic (lactic acidosis >2.0 mmol/dL), respiratory (acute lung injury [ALI] PaO2/FiO2 ≤300 [39.99 kPa] or PEEP >5 cmH2O), renal (serum creatinine [Cr] increased >1 mg/dL from baseline despite fluid resuscitation or Cr >2.0 mg/dL regardless of baseline), hepatic (acute elevation of serum bilirubin >2 mg/dL), hematologic (platelet count <100,000/mm3 or PT/PTT >1.5 times baseline), and neurologic (onset delirium or Glasgow Coma Scale <12).

Table 2. Characteristics within 24 hours of admission to the ICU

Variables	All (N=4192)	Sustained hypotension (N=212)	No hypotension (N=3980)	p value
Hemodynamic pattern				
• HR low	64 (18)	63 (27)	65 (17)	0.2
• HR high	99 (22)	110 (26)	99 (22)	<0.0001
• SBP low	107 (28)	70 (28)	108 (27)	<0.0001
• SBP high	174 (28)	155 (28)	175 (27)	<0.0001
• MAP low	73 (20)	52 (21)	74 (19)	<0.0001
• MAP high	116 (20)	107 (26)	116 (19)	<0.0001
• CI, Md (IQR) N=18	3.6 (2.6-4)	3.0 (2.5-3.8)	3.8 (2.8-4.4)	0.3
• PAOP, Md (IQR) N=16	14.5 (7-18)	10 (5-13)	16 (8-18)	0.049
• CVP, Md (IQR) N=18	10 (5-13)	5 (2-11)	11 (8-15)	0.08
• PAs, Md (IQR) N=16	33 (28-45)	26 (18-30)	37 (30-47)	0.03
• PAd, Md (IQR) N=14	16 (11-20)	10 (8-11)	16 (15-21)	0.1
• LVswi, Md (IQR) N=7	43 (33-49)	35 (27-41)	50 (45-55)	0.03
• Urinary output (L/24 hr), Md (IQR)	1.8 (1.1-2.6)	1.8 (0.9-3.2)	1.8 (1.1-2.6)	0.8
Temperature				
• Temp low	36.3 (0.8)	35.9 (1.4)	36.4 (0.8)	<0.0001
• Temp high	37.6 (0.9)	37.6 (1.4)	37.6 (0.9)	0.9
Admission WBC, cells/mL	12.2 (14)	13.3 (6.6)	12.2 (14.4)	0.3
Mechanical ventilation, N (%)	1408 (34)	123 (58)	1285 (32)	<0.0001
Measured ABGs, N(%)	1583 (38)	126 (59)	1457 (37)	<0.0001
• Arterial pH, Mean (SD)	7.44 (7.38-7.49)	7.42 (7.33-7.5)	7.44 (7.38-7.49)	0.1
• Arterial PaO2, Md (IQR)	238 (163-352)	308 (174-476)	233 (161-334)	0.001
• PaO2/FiO2, Md (IQR)	283 (193-383)	233 (144-344)	286 (198-387)	0.0003

Legend: HR=heart rate; SBP=systolic blood pressure; MAP=mean arterial pressure; CI=cardiac index; PAOP=pulmonary artery occlusion pressure; CVP=central venous pressure; PAs=pulmonary artery systolic pressure; PAd=pulmonary artery diastolic pressure; LVswi=left ventricle stroke work index; WBC=white blood cell count; Md=median; IQR=interquartile range.
LData presented as mean (SD), median (IQR), or N(%).

Table 3. Outcomes of study patients

Outcomes	All (n=4192)	Sustained hypotension (n=212)	No hypotension (n=3980)	p value
Case-fatality, N (%)	1370 (33)	152 (72)	1218 (31)	<0.0001
Survivors, N (%)				<0.0001*
• Independent	660 (16)	11 (5)	649 (16)	
• Partially dependent	1446 (35)	31 (15)	1415 (36)	
• Fully dependent	694 (17)	17 (8)	677 (17)	
ICU LOS, Md (IQR)	3 (1-6)	1.2 (1-4)	2.6 (1.3-5.7)	<0.0001
Hospital LOS, Md (IQR)	8 (4-14)	3 (2-8)	8 (4-14)	<0.0001

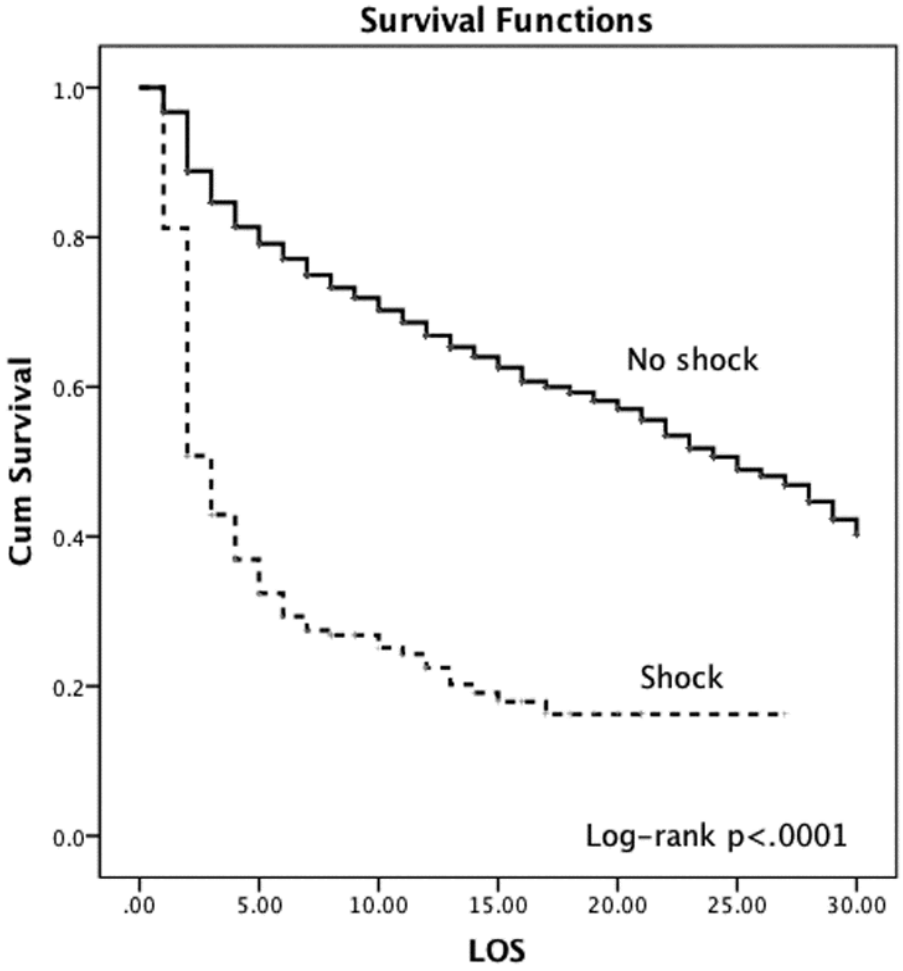
Legend: LOS=length of stay; Md=median; IQR=interquartile range; * Trend test.

Table 4. Multivariate regression model with in-hospital mortality as the dependent variable (Main effect)

Parameter	Odds ratio	95% Confidence interval		p value
		Lower	Upper	
Age	1.013	1.005	1.021	0.001
Gender (female)	0.788	0.617	1.006	0.056
DNR status	1.825	1.304	2.555	<0.001
ED boarder	1.433	0.908	2.262	0.122
APACHE II >15*	2.873	2.206	3.742	<0.001
GCS<8	11.367	8.381	15.417	<0.001
GCS 8-12	2.053	1.475	2.858	<0.001
Mechanical ventilation	1.987	1.573	2.511	<0.001
Organ dysfunction	1.695	1.431	2.042	<0.001
Fever	0.914	0.724	1.153	0.446
Hypothermia (spontaneous)	7.296	2.753	19.336	<0.001
EVD placement	0.719	0.592	0.872	0.001
Hypotension (SBP<90)	1.898	1.182	3.047	0.008
Propensity score	1.223	0.912	1.534	0.3

Legend: DNR=do not resuscitate; ED=emergency department; GCS=Glasgow coma scale; EVD=external ventricular drain; SBP=systolic blood pressure; APACHE II=acute physiologic and chronic health assessment II score.
We used generalized estimated equations (GEE) under a robust estimation technique assuming an independence working correlation matrix. Exchangeable, unstructured, and autoregressive (AR1) matrices all provided inferior fit suggesting increased risk of death in hospitals with lower patient volume for all diagnoses. We report the results of the exchangeable working correlation, which provided the best fit for the model.

Figure 1. Kaplan-Meyer survival curve for those with sustained shock versus those without shock upon admission to the ICU



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