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Association of Early Myocardial Workload and Mortality Following Severe Traumatic Brain Injury

Vijay Krishnamoorthy, MD PhD^{1,7}, Monica S. Vavilala, MD^{7,8}, Nophanan Chaikittisilpa, MD^{7,8}, Frederick P. Rivara, MD MPH^{2,4,7}, Nancy R. Temkin, PhD^{5,6,7}, Abhijit V. Lele, MD MS^{7,8}, Edward F. Gibbons, MD^{3,7}, and Ali Rowhani-Rahbar, MD MPH PhD^{2,7}

¹Department of Anesthesiology, Duke University

²Department of Epidemiology, University of Washington

³Department of Medicine, Division of Cardiology, University of Washington

⁴Department of Pediatrics, University of Washington

⁵Department of Neurosurgery, University of Washington

⁶Department of Biostatistics, University of Washington

⁷Harborview Injury Prevention and Research Center, University of Washington

⁸Department of Anesthesiology and Pain Medicine, University of Washington

Abstract

Objective—To examine the impact of early myocardial workload on in-hospital mortality following isolated severe TBI.

Design—Retrospective cohort study.

Setting—Data from the National Trauma Databank (NTDB), a multicenter trauma registry operated by the American College of Surgeons, from 2007–2014.

Patients—Adult patients with isolated severe TBI [defined as admission Glasgow Coma Scale (GCS) < 8 and head Abbreviated Injury Score (AIS) ≥ 4].

Interventions—Admission rate-pressure product (RPP), categorized into 5 levels based on published low, normal, and submaximal human thresholds: less than 5,000; 5,000 to 9,999; 10,000 to 14,999; 15,000 to 19,999; and greater than 20,000.

Measurements and Main Results—Data from 26,412 patients were analyzed. Most patients had a normal RPP (43%), 35% had elevated RPP, and 22% had depressed RPP at hospital admission. Compared to the normal RPP group, in-hospital mortality was 22 percentage points higher in the lowest RPP group (cumulative mortality 50.2%, 95% CI: 43.6% – 56.9%) and 11

Corresponding Author: Vijay Krishnamoorthy, MD PhD, Assistant Professor, Anesthesiology, Duke University, 2301 Erwin Rd., Durham, NC 27710, Phone: 919-684-8111, vijay.krishnamoorthy@duke.edu.

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percentage points higher in the highest RPP group (cumulative mortality 39.2%, 95% CI: 37.4% – 40.9%). The lowest RPP group was associated with a 50% increased risk of mortality, compared to the normal RPP group (aRR 1.50, 95% CI: 1.31–1.76, $p<0.0001$); and the highest RPP group was associated with a 25% increased risk of mortality, compared to the normal RPP group (aRR 1.25, 95% CI: 1.18 – 1.92, $p<0.0001$). This relationship was blunted with increasing age. Among patients with normotension, those with depressed and elevated RPPs experienced increased mortality.

Conclusions—Adults with severe TBI experience heterogeneous myocardial workload profiles that have a “U-shaped” relationship with mortality, even in the presence of a normal blood pressure. Our findings are novel, and suggest that cardiac performance is important following severe TBI.

Keywords

traumatic brain injury; hemodynamics; myocardial workload; trauma

Introduction

Traumatic brain injury (TBI) is a worldwide public health problem and contributes to 30% of all injury-related deaths(1). Early hemodynamic instability, including hypotension and hypertension are common in patients with severe TBI. Recent investigations have suggested that this hemodynamic profile is associated with myocardial dysfunction following TBI(2). Furthermore, early blood pressure instability is associated with poor TBI outcomes(3, 4). While early intervention for hypotension following TBI has been recommended by international TBI guidelines(5, 6), no studies have evaluated the status of the heart when making rational choices of agents to control hemodynamics following TBI. A more thorough evaluation of cardiac status following TBI has the potential to improve hemodynamic management and improve outcomes.

The rate-pressure product (RPP, the product of systolic blood pressure and heart rate) is a well-recognized and clinically useful bedside index of myocardial workload, reflecting myocardial oxygen demand and consumption(7–9). While elevated myocardial workload has been strongly associated with ischemic cardiac events in patients with heart disease(10) and during exercise(11), data on myocardial workload in the clinical neuroscience literature is limited. Yet, optimal cardiac performance is crucial to maintaining cardiac output and in turn cerebral blood flow following neurologic injury, and increased myocardial workload may eventually lead to impaired cardiac function, reduced cerebral blood flow, and poor functional outcomes(12). Therefore, the RPP may represent an easily measured bedside variable to clinically assess myocardial workload and optimize hemodynamic management following severe TBI. To further understand the impact of early myocardial workload on TBI outcomes, the study’s primary aims were to: 1) Describe the early myocardial workload profile following severe TBI, 2) Examine the association between the admission myocardial workload profile and mortality, and 3) Examine the utility of the myocardial workload profile in addition to blood pressure alone following severe TBI.

Materials and Methods

National Trauma Data Bank

Our study used data from the National Trauma Data Bank (NTDB), a national trauma registry created and operated by the American College of Surgeons. The NTDB mission is to provide the trauma community with “consistent, quality data”(13) and “to inform the medical community, the public, and decision makers about a wide variety of issues that characterize the current state of care for injured persons.”(14) The NTDB is fully de-identified and does not meet the regulatory definition of human subjects research, thus the study was exempt from IRB approval.

Study Design and Population

We conducted a retrospective cohort study using the NTDB data for the years 2007–2014. We linked all data files per year (using a unique de-identified patient number), including files for demographic data, facility data, emergency department data, injury characteristics, discharge diagnoses, procedures, and disposition. To focus on isolated severe TBI patients, we made the following exclusions: patients less than 18 years of age, patients without an International Classification of Diseases (ICD) code for TBI, patients with an emergency department Glasgow Coma Scale (GCS) score of greater than 8, and patients not admitted to the hospital. In addition to GCS, we also used the head Abbreviated Injury Score (AIS) to assess TBI severity, as it outperforms GCS score as a predictor of outcome after TBI(15); and we excluded patients with a head AIS score of less than 4, which represents the threshold for severe TBI(16). To focus on the effect of the isolated TBI on myocardial workload (and remove the confounding effects of significant blood loss and non-head injuries), we excluded patients with penetrating TBI and patients with an AIS score of greater than 2 in non-head body regions. We excluded patients with missing blood pressure or heart rate data, and patients who died within 24 hours of admission based on the rationale that early mortality was likely related to the severity of the initial neurologic injury. Lastly, we excluded patients who experienced a hospital transfer, as we wanted to capture the admission hemodynamic variables as close to the time of injury as possible, as well as final hospital discharge disposition.

Exposures, Outcomes, and Covariates

Our primary exposure of interest was the admission RPP, calculated as the admission systolic blood pressure multiplied by the heart rate. RPP thresholds for the primary analysis were chosen based on clinical studies demonstrating the mean resting and submaximal RPP thresholds patient populations that were negative for stress-induced cardiac ischemia and free of cardiovascular medications(17), and rounded to the nearest ten-thousand; thus, the reference RPP values selected were between 10,000 to 20,000. These RPP thresholds were further subdivided in the primary analysis in order to examine a dose-response effect of RPP on mortality into the following groups: less than 5,000; 5,000 to 9,999; 10,000 to 14,999; 15,000 to 19,999; and greater than 20,000. As different myocardial workloads and outcomes have not been rigorously evaluated in the neuroscience literature, we tested the robustness of the direction of the mortality risk using sensitivity analyses with differing RPP thresholds, using 7,500 and 22,500 for lower and upper limits, respectively.

In addition to detailed admission hemodynamic data, relevant demographic, clinical, and injury severity variables included age, sex, Injury Severity Score (ISS), admission total GCS score, the need for mechanical ventilation during the hospitalization, and injury mechanism. Each facility in the NTDB was assigned a unique facility identification number, allowing facility-level factors to be collected [facility size, teaching status, and trauma level designation]; clustering by facility was taken into account in all of our analyses. Our primary outcome of interest was in-hospital mortality.

In order to select appropriate variables for adjustment in our statistical models, we created directed acyclic graphs (DAG) to construct causal diagrams of the relationship between early myocardial workload and mortality using available NTDB variables; we then compared our model with data-driven confounder adjustment models of NTDB data. Our final DAG (based on existing knowledge and biologic plausibility) included variables for adjustment that closely resembled the data-driven approach for confounder adjustment in the NTDB, which suggested a parsimonious model of confounding variables that are necessary for adjustment in NTDB mortality analyses(18). All variables in our final model were included in the suggested parsimonious model, including age, gender, blood pressure and heart rate (captured in the RPP), GCS score, ISS, and mechanical ventilation.

Statistical Analysis

We described the demographic and clinical characteristics of the patient cohort, stratified by RPP categories. We further described RPP categories by hemodynamic characteristics, both as continuous and categorical variables. Continuous variables are reported as means and standard deviation; and categorical variables are reported as counts and percentages. We calculated the cumulative incidence of in-hospital mortality, stratified by RPP categories.

We calculated univariate and multivariable estimates of the association between RPP levels and in-hospital mortality using Poisson regression models with clustered robust standard error estimates, relaxing the assumption that observations from the same hospital are independent. As we hypothesized a “U-shaped” relationship between RPP level and outcome, RPP was grouped *a priori* into 5 categories, with the middle category (10,000 to 14,999) as the reference group. To assess the influence of age on the relationship between RPP levels and mortality, we conducted additional analysis stratified by age categories. We divided our cohort into blood pressure groups [hypotensive (SBP<90 mmHg), normotensive (SBP 90–140 mmHg), and hypertensive(SBP>140 mmHg)] to analyze the association between blood pressure alone versus blood pressure with a high/low RPP and in-hospital mortality; additionally, we conducted an additional multivariable analysis with both RPP and SBP included in the model, to examine the association of RPP and mortality, beyond SBP alone. We report estimates as relative risks with 95% confidence intervals. Analyses were conducted using Stata 13.0 (College Station, Texas).

Results

All patients from the NTDB from 2007 to 2014 (N=5,843,837) were initially included in the patient sample. Among these patients, 71,999 patients with severe isolated TBI were identified. After all exclusions, we derived the final cohort of 26,412 patients (Figure 1).

Demographic, Clinical, and Myocardial Workload Characteristics

Table 1 describes the demographic and clinical characteristics of the cohort, stratified by RPP categories [$<10,000$ (low RPP), $10,000$ to $15,000$ (middle RPP), $>15,000$ (high RPP)]. In all groups, the majority of patients were male (73%). The majority of patients were white (66%), and the primary injury mechanism was fall-related (43%), followed by motor-vehicle related injuries (34%). The admission GCS [mean(SD) 4.4(1.9)] score was low, suggesting severe TBI in all RPP groups. Overall, 8,316 (31%) died in-hospital.

Hemodynamic characteristics of the cohort, stratified by myocardial workload, are summarized in Table 2. In the lowest RPP group ($<5,000$), RPP was primarily driven by bradycardia (72%), while 43% of patients were normotensive. The next RPP group ($5,000 - 9,999$) included patients who were primarily normotensive (68%) and with a normal heart rate (67%). In the reference RPP group ($10,000 - 14,999$), the majority of patients had a normal heart rate (77%), and were both normotensive (48%) and hypertensive (51%). Both high RPP groups (RPP $\geq 15,000$) were primarily driven by hypertension [RPP $15,000 - 19,999$ (81%), RPP $\geq 20,000$ (97%)] and tachycardia [RPP $15,000 - 19,999$ (61%), RPP $\geq 20,000$ (91%).

Association Between Myocardial Workload and In-Hospital Mortality

The association between admission myocardial workload and in-hospital mortality is examined in Table 3. The cumulative mortality was lowest in the reference RPP group (28.1%, 95% CI: 27.3% – 29.0%), and was higher in a stepwise fashion in both the low and high RPP groups. Compared to the reference RPP group, in-hospital mortality was an absolute 22 percentage points higher in the lowest RPP group (cumulative mortality 50.2%, 95% CI: 43.6% – 56.9%) and an absolute 11 percentage points higher in the highest RPP group (cumulative mortality 39.2%, 95% CI: 37.4% – 40.9%). On multivariable regression analysis, the lowest RPP group was associated with a 50% increased risk of mortality, compared to the reference RPP group (relative risk 1.50, 95% CI: 1.31–1.76, $p<0.0001$); and the highest RPP group was associated with a 25% increased risk of mortality, compared to the reference RPP group (relative risk 1.25, 95% CI: 1.18 – 1.92, $p<0.0001$).

Figure 1 examines the association of admission myocardial workload and in-hospital mortality, stratified by the age categories of 18–44, 45–64, and ≥ 65 years. Overall, the association between admission RPP and in-hospital mortality is blunted by older age. Among the youngest patients (18–44 years), the lowest RPP category was associated with 100% increased risk of mortality (relative risk 2.00, 95% CI: 1.53 – 2.61, $p<0.0001$) and the highest RPP category was associated with a 54% increased risk of mortality (relative risk 1.54, 95% CI: 1.35 – 1.76, $p<0.0001$), compared to the reference RPP category ($10,000 - 14,999$). Among middle-age patients (45–64 years), the lowest RPP category was associated with a 63% increased risk of mortality (relative risk 1.63, 95% CI: 1.34 – 1.99, $p<0.0001$) and the highest RPP category was associated with a 22% increased risk of mortality (relative risk 1.22, 95% CI: 1.11 – 1.34, $p<0.0001$), compared to the reference RPP category. Among elderly patients (≥ 65 years), the lowest RPP category was associated with a non-significant 14% increased risk of mortality (relative risk 1.14, 95% CI: 0.93 – 1.41, $p=0.21$) and the

highest RPP category was associated with a 16% increased risk of mortality (relative risk 1.16, 95% CI: 1.09 – 1.24, $p<0.0001$), compared to the reference RPP category.

Myocardial Workload in Addition to Blood Pressure

The utility of myocardial workload among admission blood pressure categories is examined in Figure 2. Among patients with admission hypertension (Panel A), patients with an RPP $\geq 20,000$ had a 12% increased risk of mortality (relative risk 1.12, 95% CI: 1.07 – 1.18, $p<0.0001$), compared to patients with an RPP $< 20,000$. Among patients with admission normotension (Panel B), patients with an RPP $\geq 20,000$ had a 70% increased risk of mortality (relative risk 1.70, 95% CI: 1.37 – 2.13, $p<0.0001$) and patients with an RPP $< 5,000$ had a 62% increased risk of mortality (relative risk 1.62, 95% CI: 1.35 – 1.95, $p<0.0001$), compared to patients with RPP 5,000 – 19,999. Among patients with admission hypotension (Panel C), patients with an RPP $< 5,000$ did not have a significant increased risk of mortality (relative risk 1.02, 95% CI: 0.86 – 1.23, $p=0.74$), compared to patients with an RPP $\geq 5,000$. As shown in Supplemental Table 4, when both RPP and SPP are examined in the same model, RPP continues to demonstrate an independent association with in-hospital mortality at the lowest (relative risk 1.77, 95% CI: 1.52 – 2.07, $p<0.0001$) and highest (relative risk 1.09, 95% CI: 1.03 – 1.15, $p=0.003$) categories.

Discussion

The main findings of the study are: 1) Depressed and elevated myocardial workload profiles are common following isolated severe TBI, 2) The admission myocardial workload profile is associated with in-hospital mortality in a “U-shaped” fashion, and 3) The admission myocardial workload profile provides additional information beyond blood pressure in predicting in-hospital mortality following severe TBI.

Measuring myocardial workload in response to stress using RPP has been studied in the cardiology and exercise physiology literature, and prior studies have demonstrated that the RPP highly correlates with invasive measures of myocardial oxygen consumption(7, 8). The RPP represents a simple and non-invasive bedside measurement of myocardial workload. Both inadequate myocardial workload response to stress, as well as chest pain at increased myocardial workloads, have been demonstrated in patients with ischemic heart disease(17). While the mechanisms responsible for alterations in myocardial workload remain to be fully elucidated in TBI, it may represent a clinical manifestation of the catecholamine-excess state that is often triggered following severe neurologic injuries(19–21).

We found that an elevated admission myocardial workload was associated with higher in-hospital mortality, especially at RPP levels that exceed human submaximal RPP thresholds. While an elevated RPP may initially be protective by helping to maintain cerebral blood flow in the setting of impaired cerebral autoregulation (22), this may eventually become maladaptive, and contribute to myocardial dysfunction(2) and reduced cardiac output, which is a critical determinant of cerebral perfusion(12). Additionally, recent observational studies(23, 24) and a meta-analysis(25) have suggested that beta-blockers have been associated with improved outcomes following TBI, but the mechanisms remain unclear. It is possible that the catecholamine reduction and improvements in myocardial workload

conditions(26) induced by beta-blockers improve cardiac output and cerebral perfusion, although further studies are necessary to fully understand the mechanisms of beta-blockers in TBI.

In our study, we found that a reduced myocardial workload was associated with excess in-hospital mortality following severe TBI. While admission hypotension was strongly associated with mortality, it was relatively uncommon in our cohort (2.7%); in contrast, reduced myocardial workload on admission occurred more frequently (21.8%). Thus, recognizing and treating hypotension is an important principle in acute TBI care, but it may not be enough to prevent reductions in cerebral blood flow, as suboptimal myocardial workload (in the face of a normal blood pressure) may also contribute. While the traditional approach to vasopressor choice following TBI has frequently involved the use of alpha-agonists without inotropic effects (i.e. phenylephrine)(27), this may paradoxically worsen myocardial workload and cardiac output, despite normalization of blood pressure(28).

The effect of myocardial workload on mortality was blunted by older age, and there may be several reasons for this. First, older patients have a less robust hemodynamic response to exercise as compared to younger patients(29), and may not be able to generate a increased myocardial workload profile for a prolonged period in response to stress. Second, as the myocardial response to catecholamines decreases with age(30, 31), the cardiac response to catecholamine-excess may be more pronounced in the younger population. Lastly, the ideal RPP for optimal cardiac performance likely varies by age, and future studies should more closely examine RPP cut-points by age.

We found that the addition of myocardial workload data to patients with admission normotension and hypertension provided added risk-stratification for in-hospital mortality. While international guidelines emphasize that normotension is the hemodynamic goal following severe TBI(5), we found that patients with normotension and both low and high myocardial workloads did worse than patients with normotension alone. Among hypertensive patients in our cohort, patients with hypertension and an elevated myocardial workload did worse than patients with hypertension alone. Thus, our data suggests that hemodynamic goals following TBI may need to include variables beyond blood pressure alone.

There are some study limitations. First, due to the nature of an administrative dataset, granular details on patient management in the hospital were not available, such as patient prescription medication use (i.e. beta-blockers), detailed neurophysiologic data (i.e. intracranial pressure), cardiac functional data (i.e. echocardiography), and hospital treatments such as vasoactive mediations, all which may influence both RPP and outcomes. To minimize residual confounding in our analysis, we sharply restricted our cohort to define a study population of patients with isolated severe TBI, to limit the influence of non-TBI injuries on RPP. Furthermore, as we measured RPP at hospital admission (and excluded hospital transfers), we expected this variable to reflect patient physiology as close to the injury as possible and with minimal influence of hospital treatments. Second, because only admission hemodynamic variables were available in our dataset, we were unable to assess the longitudinal changes in RPP, response of RPP to hospital treatments, or the influence of

longitudinal RPP changes on mortality; thus, further studies are needed to fully understand the impact of RPP treatment on patient outcomes. Third, we were only able to capture in-hospital mortality following severe TBI; and future studies should examine long-term patient-centered outcomes beyond mortality alone, including neurocognitive and functional outcomes. Fourth, because of smaller numbers at the extremes of RPP in our cohort, potential differences in outcomes compared to the reference group have the potential to be exaggerated. Lastly, due the observational nature of our study, it is impossible to fully establish a causal link of myocardial workload on mortality from our study alone (rather than the myocardial workload being a biomarker of injury severity), and further studies in heterogeneous TBI populations are needed to confirm our findings and fully understand the causal impact of myocardial workload, and its potential treatment, on TBI outcomes.

Conclusion

The admission myocardial workload profile is associated with in-hospital mortality following severe TBI in a “U-shaped” fashion. Our findings are novel, and suggest that cardiac performance is important following severe TBI. Future studies should more closely evaluate cardiac function following severe TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Association of admission myocardial workload and in-hospital mortality, stratified by the age categories of 18–44, 45–64, and ≥ 65 years

A. Hypertension (SBP > 140mmHg): **B. Normotension (SBP 90-140 mmHg):** **C. Hypotension (SBP < 90 mmHg):** **Figure 2.**

Association of admission myocardial workload and in-hospital mortality among patients with admission hypertension (Panel A), normotension (Panel B), and hypotension (Panel C)

Table 1 Demographic and Clinical Characteristics of Patients with Isolated Severe TBI^{*,**}

Rate-Pressure Product	Total	< 10,000	10,000 – 14,999	> 15,000
N	26,412 (100%)	5,753 (21.8%)	11,343 (42.9%)	9,316 (35.3%)
Age (years)		46.1 ± 20.2	47.7 ± 20.5	51.2 ± 20.6
18–44	11,591 (43.9%)	2,855 (49.6%)	5,228 (46.1%)	3,508 (37.7%)
45–64	7,818 (29.8%)	1,619 (28.1%)	3,318 (29.3%)	2,941 (31.6%)
65	6,355 (24.1%)	1,173 (20.4%)	2,580 (22.8%)	2,602 (27.9%)
Male	19,289 (73.0%)	4,173 (72.5%)	8,317 (73.3%)	6,799 (73.0%)
Race				
White	17,392 (65.9%)	3,815 (66.3%)	7,533 (66.4%)	6,044 (64.9%)
Hispanic	3,298 (12.5%)	730 (12.7%)	1,390 (12.3%)	1,178 (12.6%)
African American	2,993 (11.3%)	614 (10.7%)	1,208 (10.7%)	1,171 (12.6%)
Asian/PI	718 (2.7%)	138 (2.4%)	328 (2.8%)	259 (2.8%)
Other	1,135 (4.3%)	246 (4.3%)	494 (4.4%)	388 (4.2%)
Missing	876 (3.3%)	210 (3.7%)	390 (3.4%)	276 (3.0%)
Injury Mechanism				
Motor – vehicle related	8,876 (33.6%)	2,035 (35.4%)	3,990 (35.2%)	2,851 (30.6%)
Fall	11,278 (42.7%)	2,235 (38.9%)	4,625 (40.8%)	4,418 (47.4%)
Transport, other	1,964 (7.4%)	496 (8.6%)	879 (7.8%)	589 (6.3%)
Struck by/against	2,158 (8.2%)	497 (8.6%)	982 (8.7%)	679 (7.3%)
Other	2,136 (8.1%)	490 (8.5%)	867 (7.6%)	779 (8.4%)
Admission GCS Score	4.4 ± 1.9	4.2 ± 1.8	4.5 ± 1.9	4.5 ± 1.8
Head AIS Score	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4
Injury Severity Score	18.0 ± 9.1	18.5 ± 9.3	17.8 ± 9.2	18.1 ± 8.9

* Data are presented as mean ± SD and counts(percentage)

** Column percentage do not add up to 100% in some categories due to missing data

GCS=Glasgow Coma Scale; AIS=Abbreviated Injury Scale

Table 2

Hemodynamic Characteristics Stratified by Rate-Pressure Product*

Rate-Pressure Product	< 5,000	5,000–9,999	10000–14,999	15,000–19,999	20,000
N	299 (0.9%)	5,524 (21.0%)	11,343 (42.9%)	6,288 (23.8%)	3,028 (11.5%)
Systolic Blood Pressure (mmHg)					
< 90	89 ± 31	123 ± 26	144 ± 26	165 ± 28	191 ± 30
	117 (51.1%)	477 (8.6%)	105 (0.9%)	1 (0.0%)	0 (0.0%)
90–140	98 (42.8%)	3,749 (67.9%)	5,444 (48.0%)	1,211 (19.3%)	103 (3.4%)
> 140	14 (6.1%)	1,298 (23.5%)	5,794 (51.1%)	5,076 (80.7%)	2,925 (96.6%)
Heart Rate (bpm)					
< 60	51 ± 19	69 ± 16	89 ± 17	107 ± 18	127 ± 22
	165 (72.1%)	1,558 (28.2%)	243 (2.1%)	0 (0.0%)	0 (0.0%)
60–100	62 (27.1%)	3,723 (67.4%)	8,727 (76.9%)	2,436 (38.7%)	262 (8.7%)
> 100	2 (0.9%)	243 (4.4%)	2,373 (20.9%)	3,852 (61.3%)	2,766 (91.4%)

* Data are presented as mean ± SD and counts(percentage)

mmHg=millimeters of mercury; bpm=beats per minute

Table 3

Association of Admission Rate-Pressure Product with In-Hospital Mortality

Rate-Pressure Product	Total	No. of Deaths	Cumulative mortality	95 % CI	Univariable		Multivariable*	
					Relative Risk	95 % CI	Relative Risk	95% CI
< 5,000	229	115	50.2%	43.6% – 56.9%	1.79	1.54–2.07	1.50	1.31–1.76
5,000–9,999	5,524	1,816	32.9%	31.6% – 34.1%	1.17	1.11–1.23	1.16	1.11–1.22
10,000–14,999 (ref)	11,343	3,190	28.1%	27.3% – 29.0%	1.0	Ref	1.0	Ref
15,000–19,999	6,288	2,009	32.0%	30.8% – 31.1%	1.14	1.08–1.19	1.07	1.02–1.12
> 20,000	3,028	1,186	39.2%	37.4% – 40.9%	1.39	1.32–1.47	1.25	1.18–1.92

* Adjusted for age, gender, injury severity score, admission Glasgow coma scale, need for mechanical ventilation