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Interrogating a clinical database to study treatment of hypotension in the critically ill

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Abstract

Objective: In intensive care, it is imperative to resolve hypotensive episodes (HEs) in a timely manner to minimize end-organ damage. Clinical practice guidelines generally recommend initial treatment with fluid resuscitation followed by vasopressor administration if patients remain hypotensive. However, the impact of such interventions on patient outcomes has not been clearly established. Hence, the objective of this study was to investigate the relationship between fluid and vasopressor interventions and patient outcomes, while highlighting the utility of electronic medical records in clinical research.

Design: Retrospective cohort study.

Setting: Intensive care units (ICUs) at a large, academic, tertiary medical center.

Participants: Patients in MIMIC-II (a large electronic ICU database) who experienced a single HE during their ICU stay.

Primary and secondary outcome measures: The primary outcome of interest was in-hospital mortality. Secondary outcomes were ICU length of stay (LOS), HE duration, Hypotension Severity Index (HSI) (defined as the MAP curve area below 60mmHg during the HE), and rise in serum creatinine.

Results: Fluid resuscitation was associated with significantly shorter ICU LOS ($p=0.007$). Vasopressor administration significantly decreased HE duration ($p<0.001$) and HSI ($p=0.002$) but was associated with increased in-hospital mortality risk ($p<0.001$), prolonged ICU LOS ($p=0.04$), and rise in serum creatinine ($p=0.002$) after adjustment for confounders. Propensity score analyses as well as sensitivity analyses in treatment- and diagnosis-specific sub-populations corroborated the relationship between vasopressors and increased in-hospital mortality.

Conclusions: An adverse relationship between vasopressors and in-hospital mortality was found in patients with hypotension. This study has implications for the care of critically ill patients with hypotension but also illustrates the utility of electronic medical records in research when randomized

controlled trials are difficult to conduct.

Article Summary

Article focus:

- To investigate the impact of fluid resuscitation and vasopressor therapy on patient outcomes in critically ill patients who experienced a hypotensive episode, using an electronic database
- To emphasize the utility of electronic medical records in clinical research when prospective randomized clinical trial results are absent

Key messages:

- Vasopressors were found to be correlated with increased in-hospital mortality risk, even after propensity adjustment.
- Electronic medical records can help answer clinical questions for which clinical trials are challenging to conduct.

Strengths and limitations of this study:

- The adverse relationship between vasopressors and in-hospital mortality was carefully established using propensity score and sensitivity analyses.
- The results of this paper are thought-provoking but inconclusive. It is possible that vasopressors harm only a specific subset of the critically ill.

Introduction

Electronic medical records (EMRs) that include detailed information on clinical care afford researchers a

unique opportunity to evaluate both practice variation and the impact of diagnostic and therapeutic decisions on patient outcomes. When compiled into clinical databases and used for research purposes, they have potential advantages compared to randomized controlled trials (RCT). For example, clinical databases built using EMRs require fewer resources to mobilize for analysis, are capable of including readily-accessible information on large and diverse patient populations, and allow research questions to be answered within a shorter period of time. Their versatility also makes them a potential resource for policymakers, as public and private healthcare payers increasingly rely on clinical evidence to support practice guidelines and coverage decisions.

The Multi-parameter Intelligent Monitoring in Intensive Care II (MIMIC-II) database (1) is a clinical database that provides detailed information about the care of patients treated in intensive care units (ICUs). Critically ill patients are an ideal population for clinical database investigations because the clinical value of many treatments and interventions they receive is unproven, and high-quality data supporting or discouraging specific practices is relatively sparse (2,3). We used MIMIC-II to explore practice variation and health outcomes in critically ill patients admitted for or later developing hypotension in an ICU. Hypotension is an important condition to study in this setting because it is a risk factor for hospital mortality and approaches to its treatment vary widely (e.g., colloids vs. crystalloids for fluid resuscitation (4,5)). Moreover, many of the interventions used to treat hypotension are associated with adverse events including pulmonary edema, heart failure, and tissue ischemia (6–9).

Methods

Study Population

This study utilized the MIMIC-II database (version 2.6), a publicly available clinical database developed through a collaboration among Massachusetts Institute of Technology (MIT), Philips Healthcare, and

Beth Israel Deaconess Medical Center (BIDMC) (1). MIMIC-II is a repository of de-identified physiologic, laboratory, and survival outcome data from over 30,000 critically ill patients cared for in ICUs at BIDMC between 2001 and 2008. These data include clinical variables such as patient age, gender, and chronic disease diagnoses as represented by International Classification of Diseases (ICD) codes; laboratory data such as hematocrit, creatinine, and electrolytes; physiologic data such as blood pressure and heart rate; markers of treatment intensity such as the utilization of invasive and noninvasive mechanical ventilation, renal-replacement therapy, central venous lines, vasopressors, and blood transfusion; and survival during and after the hospitalization.

Patients in MIMIC-II who were cared for in medical ICUs (MICU), surgical ICUs (SICU), coronary care units (CCU), and cardiac surgery recovery units (CSRU) were included in the study. In addition, patients were eligible for inclusion in this study if they experienced a single hypotensive episode (HE) and their code status was not comfort-measures-only within 24 hours before and after the HE. Hypotension was defined based on mean arterial pressure (MAP) measurements obtained either by invasive arterial catheters or non-invasive sphygmomanometers, usually recorded every 10-15 minutes for our cohort. The beginning of an HE was defined as the time of the first of two consecutive MAP measurements less than or equal to 60 mmHg, preceded by two consecutive MAP values above 60 mmHg. The end of an HE was defined as the time of the first of two consecutive MAP measurements greater than 60 mmHg, preceded by two consecutive MAP values less than or equal to 60 mmHg. A MAP threshold of 60 mmHg was used in the study based on the finding that autoregulation ceases and blood flow becomes pressure dependent below this level in various organs (10).

Study Variables and Outcomes

The two primary variables of interest were administration of intravenous fluid and initiation or increase in dosage of vasopressor agents during the HE. Fluid resuscitation was defined as at least one infusion of either a bolus of isotonic crystalloid of at least 250 ml or any volume of colloids. Vasopressor therapy was

defined as an initiation or a dosage increase of dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine, or vasopressin during the HE. Not all patients received fluids or vasopressors during their HE.

The primary patient outcome was in-hospital mortality, while the secondary outcomes were ICU length of stay (LOS) longer than 3 days, HE duration longer than 1 hour, Hypotension Severity Index (HSI), defined as the MAP curve area below 60 mmHg during the HE, and any increase in serum creatinine level within three days following the HE. Figure 1 illustrates how we calculated HSI for each HE. HSI approximates the area between linearly interpolated mean blood pressure measurements and the 60 mmHg and captures both HE duration and magnitude of blood pressure in one metric. The unit of HSI is mmHg·min. As an outcome variable, HSI was first calculated as a continuous value and subsequently dichotomized with a threshold of 150 mmHg·min. ICU LOS was investigated only among the patients who survived the ICU stay.

Control variables in this study included age, gender, Simplified Acute Physiologic Score (SAPS) (a predictor of mortality for critically ill patients), an Elixhauser comorbidity score (11) calculated using the method described by Walraven et al (12), mean MAP in the 3-hour period immediately prior to the HE onset, total volume of urine output in the 3-hour period immediately prior to the HE onset greater than 200 ml, last serum creatinine level prior to and within 24 hours of the HE onset, and service type (MICU, SICU, CCU, or CSRU).

Statistical Analysis

The effects of hypotension treatment approaches on patient outcomes were investigated after adjusting for confounding variables using multivariate logistic regression. For each logistic regression model, the Hosmer-Lemeshow (H-L) goodness-of-fit test (13) and receiver operating characteristic (ROC) curve analysis were performed to evaluate the calibration and discrimination of the model, respectively. For all

outcomes, p-values less than 0.05 were considered significant.

In order to further address omitted variable bias in the in-hospital mortality analysis, a propensity score analysis (14) was employed to adjust for the likelihood of receiving vasopressor therapy. A logistic regression model with all control variables was built to estimate propensity scores for receipt of vasopressor therapy. Propensity scores were then used in a subsequent regression model as a regressor along with the primary predictors (fluids and vasopressors), while the outcome variable was in-hospital mortality.

As a sensitivity analysis, in-hospital mortality with and without adjustment using propensity scores was analyzed after excluding patients who received neither fluids nor vasopressors during their HE. By focusing only on treated patients, patients with a potentially clinically unimportant HE were excluded. Similarly, in-hospital mortality with and without propensity score adjustment was also investigated within patients who received either only fluids or both fluids and vasopressors (in other words, fluid resuscitated patients). By excluding patients who received only vasopressors and no fluids during their HE, this sensitivity analysis reduced the number of patients whose clinical presentations were more severe.

We also performed subgroup analyses among patients with sepsis and among patients with congestive heart failure (CHF) based on ICD-9 codes. The rationale was to address potential bias by indication. Separate logistic regression models with propensity score adjustment were constructed for these analyses.

All statistical analyses were performed using MATLAB version R2010b (MathWorks, Natick, MA).

Results

A total of 3,163 patients in MIMIC-II met the inclusion criteria. Of these patients, 63.3% and 81.6% developed an HE within 24 and 48 hours of ICU admission, respectively. Table 1 summarizes the demographic and clinical characteristics of the patients in our cohort. The median HE duration was 2

hours. Most HEs (62.9%) were treated with neither fluids nor vasopressors, whereas 19.8% of the patients were fluid resuscitated. The incidence of vasopressor use was 17.3% as monotherapy and 6.3% in combination with fluids. The in-hospital mortality of the patient cohort was 12.9%, while the median ICU LOS was 2.7 days. Of the 3,163 patients, 732 and 354 were CHF and sepsis patients, respectively.

Table 2 summarizes results for in-hospital mortality stratified by treatment. Of the 3,163 patients, 2,332 had complete data and were included in multivariate analyses. The largest contributor to missing data was serum creatinine. While no significant relationship was found between fluid resuscitation and in-hospital mortality, vasopressor therapy was associated with an increased in-hospital mortality risk in all (odds ratio (OR)=2.86, p<0.001), treated (received either fluids or vasopressors, or both) (OR=2.41, p=0.02), and fluid resuscitated patients (received either only fluids or both fluids and vasopressors) (OR=2.30, p=0.04). Among the control variables, older age, higher SAPS, higher Elixhauser, higher mean MAP prior to the HE, lower urine output prior to the HE, and MICU (in comparison to SICU, CCU, and CSRU) were significantly associated with higher in-hospital mortality in the overall cohort. Among the treated patients only, higher SAPS, higher Elixhauser, lower urine output prior to the HE, and MICU (in comparison to CSRU) were associated with higher in-hospital mortality. The multivariate analysis of fluid resuscitated patients showed that higher SAPS, higher Elixhauser, lower urine output prior to the HE, and MICU (in comparison to CCU and CSRU) were all associated with an increased risk of death.

In estimating the propensity for vasopressor therapy in the entire patient cohort, younger age, male gender, higher SAPS, higher Elixhauser, lower urine output prior to the HE, and CSRU (in comparison to MICU) were significantly correlated with higher likelihood of receiving vasopressors. In the treated patients, higher SAPS, higher Elixhauser, higher serum creatinine prior to the HE, and CSRU (in comparison with MICU) were significant predictors of vasopressor therapy. Among the patients who received fluid resuscitation, higher SAPS, higher serum creatinine prior to the HE, and CSRU (in comparison with MICU) were associated with increased propensity. See Appendix for detailed results of the propensity score calculation models.

Table 3 summarizes the relationship between vasopressor therapy and in-hospital mortality after propensity score adjustment. Vasopressor therapy remained significantly associated with increased mortality, in all (OR=2.44, p<0.001), treated (OR=2.20, p=0.009), and fluid resuscitated patients (OR=1.02, p=0.02). However, in comparison with our results in Table 2, the corresponding vasopressor ORs for in-hospital mortality decreased, most substantially in patients who received fluid resuscitation (from 2.30 to 1.02).

Our subgroup analyses yielded similar findings as the main analyses. In the 732 patients with CHF, vasopressor therapy remained significantly correlated with in-hospital mortality after propensity score adjustment (OR=2.00, p=0.004). Likewise, in the 354 sepsis patients, vasopressor therapy was a significant predictor of in-hospital mortality with (OR=2.84, p<0.001) after propensity score adjustment.

Table 4 provides the multivariate logistic regression results for the secondary outcomes in all patients. We found that fluid resuscitation was significantly associated with shorter ICU LOS (OR=0.71, p=0.007) and greater HSI (OR=1.26, p=0.04). Vasopressor administration was significantly associated with longer ICU LOS (OR=1.29, p=0.04), shorter HE duration (OR=0.29, p<0.001), decreased HSI (OR=0.72, p=0.002), and rise in serum creatinine (OR=1.44, p=0.002). Among other demographic and clinical variables, older age was significantly related to shorter ICU LOS and greater HSI. Higher SAPS and lower urine output prior to the HE were significantly correlated with longer ICU LOS, shorter HE duration, and rise in serum creatinine. Higher Elixhauser comorbidity scores were linked to longer ICU LOS and rise in serum creatinine. Higher mean MAP prior to the HE was significantly associated with longer ICU LOS, shorter HE duration, and lower HSI.

Discussion

Clinical databases built using EMRs such as MIMIC-II represent an opportunity to study clinical areas where practice variation exists or care standards have not been established. In this study, we examined

treatment of hypotension in the ICU. The decision to administer intravenous fluids or vasopressors, and the volume or dose chosen, largely depend on the clinician's preferences and practice patterns within an ICU, along with process-related factors at the time of the hypotensive event (e.g., physician presence at the bedside, nurse-to-patient ratio, etc.) (15). Clinician decision-making, in the absence of strong guidelines, is frequently driven by prior experience, which is particularly prevalent in intensive care where RCT evidence is relatively sparse (16,17). This results in significant care variability not explained by patient or contextual factors but instead driven by individual provider practice. Use of inotropes, for example, has been described as both hospital- and physician-dependent, being administered to as few as 5% or to as many as 100% of patients undergoing elective cardiac surgery (18,19).

In our retrospective analysis, we did not find significant variation in the rate of fluid administration, with majority of the patients receiving between 250 and 500 ml/hr. The limited variability in fluid administration volume may explain why we did not find a relationship between fluid administration and in-hospital mortality or most of our secondary outcomes. The administration of vasopressors, however, was an independent predictor of in-hospital mortality, and this relationship persisted in the propensity score analysis. To address the issue of confounding by indication, multivariate logistic regression and propensity score analyses were performed in subsets of patients with CHF or sepsis. In all of these analyses, vasopressor use remained independently associated with in-hospital mortality.

Other studies have also reported that vasopressor therapy may be associated with higher mortality. Shahin and colleagues (20) found that hospital mortality and renal dysfunction were consistently lower in patients unexposed to inotropes, even when their six-hour physiologic variables were lower than literature-recommended targets. In patients with heart failure, a systematic review of controlled trials of catecholaminergic agents compared to placebo found no improvement in patient outcomes—indeed, there was evidence of harm (21). Using data from the multi-center trial of L-NMMA in septic shock, Dunser et al (22) found that mean vasopressor load was associated with higher 28-day mortality.

Catecholamines have a wide range of potential adverse effects (6), including excess vasoconstriction and impaired microcirculation leading to impaired organ perfusion and increased metabolic demands, including myocardial oxygen requirement. Furthermore, catecholamine use has been associated with reduced metabolic efficiency by promoting fatty acid oxidation. Catecholamines have also been associated with increased bacterial virulence and biofilm formation and altered immune response (6,23,24).

Clinical databases built using EMRs may be ideal resources for evaluating the impact of vasopressors on outcomes. Randomized placebo-controlled clinical trials for commonly used vasopressors are either unavailable or lack sufficient statistical power to evaluate differences in important clinical outcomes (25). Our study was not able to address whether the observed increase in hospital mortality was more likely to occur with some vasopressors than others due to inadequate power.

It is important to note that, despite our use of propensity scores, residual confounding remains a concern. We attempted to address this by repeating our analyses in patient subsets but we may not have fully adjusted for severity of illness. Little data elsewhere exist that examine the impact of vasopressors on end-organ preservation. This area may be a promising one for clinical trials.

Alternative interpretations of our findings are possible. It may be that the adverse relationship between vasopressors and survival actually comprises a combination of incremental benefits in a subset of patients that are outweighed by incremental harms in another subset. The threshold blood pressure below which end-organ damage ensues likely differs among patients, and perhaps even within the same patient in different clinical contexts. The clinical challenge is to predict the lowest blood pressure threshold for which no treatment is required. The concept of permissive hypotension has been introduced in the neonatal intensive care literature based on findings of similar outcomes between normotensive and hypotensive low birth weight infants with signs of good perfusion (26). Permissive hypotension would be challenging to investigate prospectively; however, analyses with robust electronic medical records may

hold the key to unraveling this conundrum.

Our study is a first step in examining management of hypotension in the ICU, and it suggests potential areas of investigation and standardization of processes of care. The frequency of vasopressor use in the ICU may have engendered a perception of safety. Titration of hemodynamic interventions such as vasopressor therapy using a fixed blood pressure target is straightforward to apply at the bedside and likely perceived as rewarding to the staff. Personalized guidelines that are patient- and context-specific may be more beneficial, particularly when treatment is associated with significant harm. Robust customization of hypotensive thresholds may be best achieved by utilizing extensive real-time modeling of physiologic variables on a patient-by-patient basis. Prospectively, prediction of outcomes with vasopressor therapy may be sought with the help of growing clinical databases to create treatment algorithms.

In a previous study, Celi et al (27) introduced a method of designing decision support tools based on a hospital's own clinical database as an alternative to expert systems derived from large, multi-center, interventional or observational studies. Using the term "Collective Experience" to refer to the aggregation of patient care data from clinicians working in a single institution, they proposed developing guideline models from a more homogeneous group of patients because of the tradeoff between generalizability and accuracy. The utility of a local EMR in clinical decision support when the existing literature lacks relevant evidence was also discussed by Frankovich et al (28). Clinical guidelines developed by a single institution may provide diagnostic assistance, treatment guidance, and prognostic capabilities that are more personalized and appropriate for an institution's patient population. The vision is a data-fueled learning system that aggregates and analyzes day-to-day experimentations, where new knowledge is constantly extracted and propagated for quality improvement, and where practice is driven by outcomes, and less so by individual clinician knowledge base and experience and the local medical culture.

Conclusions

Using an EMR, we found that patients who were exposed to vasopressor therapy during hypotensive episodes were more likely to die, a finding consistent with other studies in sepsis, cardiac surgery, and heart failure. Clinical databases such as MIMIC-II can complement knowledge gained from conventional comparative-effectiveness research methods and provide important insights about routine patient care.

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Competing Interests

All authors declare that there is no competing interest associated with this research.

Data Sharing

There is no additional data available. This study was conducted based on the public MIMIC-II database. Any interested researcher can gain access to MIMIC-II; for details, please see http://physionet.org/mimic2/.

Contributors

JL designed the study, conducted data extraction and analyses, and wrote most parts of the manuscript. RK designed the study, helped with data extraction, and critically revised the manuscript. JAL wrote the

discussion section and critically revised the manuscript. DJS helped with data extraction and critically revised the manuscript. LAC designed the study, wrote the discussion section, and critically revised the manuscript. JL and LAC are the guarantors of the study. All authors had full access to all of the data.

Figure Captions

Figure 1: A pictorial illustration of Hypotension Severity Index (HSI) calculation. The grayed area in mmHg·min represents the HSI in this particular case. Consecutive mean blood pressure measurements are linearly interpolated, and the area below 60 mmHg from the first to last measurement of the HE is computed. HSI has the advantage of harnessing both magnitude of mean blood pressure and HE duration.

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Table 1: Demographic and clinical characteristics of the study population (N=3163).

Age* (yr)		69.3 [56.9,79.3]
Gender (male)		54.3%
Service type		
	MICU	33.2%
	SICU	22.0%
	CCU	15.8%
	CSRU	29.0%
SAPS I*		15 [11,19]
HE duration* (min)		120 [45,120]
Hypotension treatment		
	No intervention	62.9%
	Fluids only	13.5%
	Vasopressors only	17.3%
	Both fluids and vasopressors	6.3%
In-hospital mortality		12.9%
ICU LOS* (days)		2.7 [1.6,4.9]
Elixhauser comorbidities		
	Congestive heart failure	20.9%
	Cardiac arrhythmias	21.0%

Valvular disease	8.6%
Pulmonary circulation disorders	2.4%
Peripheral vascular disorders	9.5%
Hypertension	30.9%
Paralysis	1.1%
Other neurological disorders	3.3%
Chronic pulmonary disease	16.4%
Diabetes, uncomplicated	21.2%
Diabetes, complicated	4.8%
Hypothyroidism	8.7%
Renal failure	5.1%
Liver disease	4.6%
Peptic ulcer disease excluding bleeding	0.5%
AIDS	0.6%
Lymphoma	1.5%
Metastatic cancer	4.4%
Solid tumor without metastasis	10.8%
Rheumatoid arthritis/collagen vascular disease	2.2%
Coagulopathy	6.1%
Obesity	1.6%
Weight loss	2.7%

Fluid and electrolyte disorders	24.3%
Blood loss anemia	0%
Deficiency anemias	11.9%
Alcohol abuse	3.7%
Drug abuse	1.8%
Psychoses	2.3%
Depression	4.1%

* median [Q_1,Q_3]

MICU: medical intensive care unit, SICU: surgical intensive care unit, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, LOS: length of stay, HE: hypotensive episode

Table 2: Multivariate logistic regression results for in-hospital mortality, shown in odds ratio (95% CI). Each column represents a separate regression model for a specific patient cohort. Treated patients received either fluids or vasopressors, or both. Fluid resuscitated patients received either only fluids or both fluids and vasopressors.

	All patients	Treated patients	Fluid resuscitated patients
Fluid resuscitation	0.87 (0.61-1.26)	0.75 (0.40-1.40)	N/A
Use of vasopressor	2.86* (2.09-3.92)	2.41* (1.19-4.88)	2.30* (1.05-5.03)
Age (yr)	1.01* (1.00-1.02)	1.01 (0.99-1.02)	1.02 (1.00-1.05)
Gender (male)	0.96 (0.72-1.27)	0.93 (0.59-1.47)	0.82 (0.40-1.67)
SAPS	1.14* (1.11-1.18)	1.17* (1.12-1.22)	1.18* (1.10-1.27)
Elixhauser	1.24* (1.14-1.36)	1.15* (1.01-1.32)	2.00* (1.26-3.17)
Mean MAP prior to HE (mmHg)	1.02* (1.00-1.03)	1.02 (1.00-1.04)	1.02 (0.99-1.06)
Urine output prior to HE > 200ml	0.65* (0.49-0.87)	0.57* (0.35-0.91)	0.30* (0.13-0.68)
Creatinine prior to HE (mg/dl)	1.07 (0.96-1.19)	1.07 (0.90-1.28)	1.05 (0.75-1.49)
Service type			
MICU**	1	1	1
SICU	0.62* (0.43-0.88)	0.62 (0.35-1.08)	0.37* (0.15-0.91)
CCU	0.63* (0.42-0.94)	0.61 (0.32-1.14)	0.25* (0.07-0.86)
CSRU	0.08* (0.05-0.14)	0.05* (0.02-0.11)	0.14* (0.05-0.41)
Number of subjects	2332	812	409

	All patients	Treated patients	Fluid resuscitated patients
AUC	0.831	0.868	0.877
Hosmer-Lemeshow p-value	0.37	0.40	0.86

* Statistically significant

** Reference

CI: confidence interval, SAPS: Simplified Acute Physiology Score, MAP: mean arterial pressure, HE: hypotensive episode, MICU: medical intensive care unit, SICU: surgical intensive care unit, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, AUC: area under the receiver operating characteristic curve, N/A: not applicable

Table 3: Vasopressor propensity score analysis results for in-hospital mortality, shown in odds ratio (95% CI). Each column represents a separate regression model for a specific patient cohort. Treated patients received either fluids or vasopressors, or both. Fluid resuscitated patients received either only fluids or both fluids and vasopressors.

	All patients	Treated patients	Fluid resuscitated patients
Fluid resuscitation	0.97 (0.70-1.33)	0.87 (0.54-1.41)	N/A
Use of vasopressor	2.44* (1.85-3.20)	2.20* (1.22-4.00)	1.02* (1.00-1.05)
Propensity for vasopressor therapy	2.04 (0.83-5.02)	0.99 (0.29-3.34)	5.01* (1.02-24.58)
Number of subjects	2332	812	409
AUC	0.621	0.601	0.628
Hosmer-Lemeshow p-value	0.01	0.01	0.28

* Statistically significant

AUC: area under the receiver operating characteristic curve, N/A: not applicable

Table 4: Multivariate regression results for the secondary outcomes in all patients, shown in odds ratio (95% CI). Each column represents a separate regression model for each secondary outcome variable.

	ICU LOS > 3 days	HE duration > 1 hr	HSI > 150 mmHg·min	Rise in serum creatinine
Fluid resuscitation	0.71* (0.55-0.91)	0.89 (0.70-1.14)	1.26* (1.01-1.57)	1.14 (0.90-1.45)
Use of vasopressor	1.29* (1.01-1.65)	0.29* (0.23-0.36)	0.72* (0.59-0.89)	1.44* (1.15-1.80)
Age (yr)	0.99* (0.99-1.00)	1.00 (1.00-1.01)	1.01* (1.00-1.01)	1.01 (1.00-1.01)
Gender (male)	0.99 (0.81-1.20)	0.83 (0.69-1.01)	0.85 (0.71-1.01)	1.07 (0.88-1.29)
SAPS	1.13* (1.10-1.15)	0.96* (0.94-0.98)	0.99 (0.97-1.01)	1.02* (1.00-1.04)
Elixhauser	1.23* (1.17-1.29)	1.19 (0.95-1.48)	1.13 (1.00-1.27)	2.14* (1.30-3.52)
Mean MAP prior to HE (mmHg)	1.04* (1.03-1.05)	0.95* (0.94-0.96)	0.98* (0.97-0.99)	1.00 (0.99-1.01)
Urine output prior to HE > 200ml	0.76* (0.63-0.92)	1.29* (1.06-1.56)	1.10 (0.92-1.30)	0.75* (0.62-0.90)
Creatinine prior to HE (mg/dl)	1.05 (0.95-1.15)	0.98 (0.90-1.07)	0.99 (0.92-1.08)	1.01 (0.92-1.11)
Service type				
MICU**	1	1	1	1
SICU	1.62* (1.23-2.13)	0.77 (0.59-1.01)	0.76* (0.60-0.97)	1.00 (0.78-1.29)
CCU	1.34 (0.99-1.81)	0.70* (0.52-0.94)	0.78 (0.60-1.02)	1.23 (0.93-1.63)

	ICU LOS > 3 days	HE duration > 1 hr	HSI > 150 mmHg·min	Rise in serum creatinine
CSRU	0.58* (0.44-0.76)	0.65* (0.50-0.84)	0.58* (0.46-0.74)	1.99* (1.55-2.56)
Number of subjects	2114	2332	2332	1989
AUC	0.721	0.733	0.624	0.635
Hosmer-Lemeshow p-value	0.42	0.02	0.16	0.69

* Statistically significant

** Reference

CI: confidence interval, SAPS: Simplified Acute Physiology Score, MAP: mean arterial pressure, HE: hypotensive episode, ICU: intensive care unit, MICU: medical ICU, SICU: surgical ICU, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, LOS: length of stay, AUC: area under the receiver operating characteristic curve

Appendix

The table below summarizes the relationships between demographic/clinical variables and the propensity for receipt of vasopressor therapy, shown in odds ratio (95% CI). Each column represents a separate propensity score model for a specific patient cohort. Treated patients received either fluids or vasopressors, or both. Fluid resuscitated patients received either only fluids or both fluids and vasopressors.

	All patients	Treated patients	Fluid resuscitated patients
Age (yr)	0.99* (0.99-1.00)	0.99 (0.98-1.01)	0.99 (0.98-1.01)
Gender (male)	1.55* (1.25-1.92)	1.21 (0.87-1.67)	1.33 (0.82-2.16)
SAPS	1.12* (1.09-1.14)	1.09* (1.06-1.13)	1.12* (1.07-1.17)
Elixhauser	1.08* (1.01-1.17)	1.29* (1.02-1.64)	N/A
Mean MAP prior to HE (mmHg)	1.01 (0.99-1.02)	1.01 (0.99-1.03)	1.00 (0.98-1.03)
Urine output prior to HE > 200ml	0.71* (0.57-0.88)	0.85 (0.61-1.17)	0.98 (0.60-1.60)
Creatinine prior to HE (mg/dl)	1.02 (0.92-1.12)	1.28* (1.08-1.53)	1.29* (1.02-1.63)
Service type			
MICU**	1	1	1
SICU	0.74 (0.53-1.03)	0.95 (0.60-1.50)	1.26 (0.63-2.51)
CCU	1.37 (0.97-1.94)	1.69 (1.00-2.85)	1.42 (0.59-3.39)
CSRU	2.07* (1.55-2.75)	2.85* (1.88-4.33)	3.53* (1.90-6.55)
Number of subjects	2332	812	409

	All patients	Treated patients	Fluid resuscitated patients
AUC	0.726	0.703	0.728
Hosmer-Lemeshow p-value	0.04	0.06	0.30

* Statistically significant

** Reference

CI: confidence interval, SAPS: Simplified Acute Physiology Score, MAP: mean arterial pressure, HE: hypotensive episode, MICU: medical intensive care unit, SICU: surgical intensive care unit, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, AUC: area under the receiver operating characteristic curve, N/A: not applicable (due to a lack of significant relationship with receipt of vasopressor therapy)

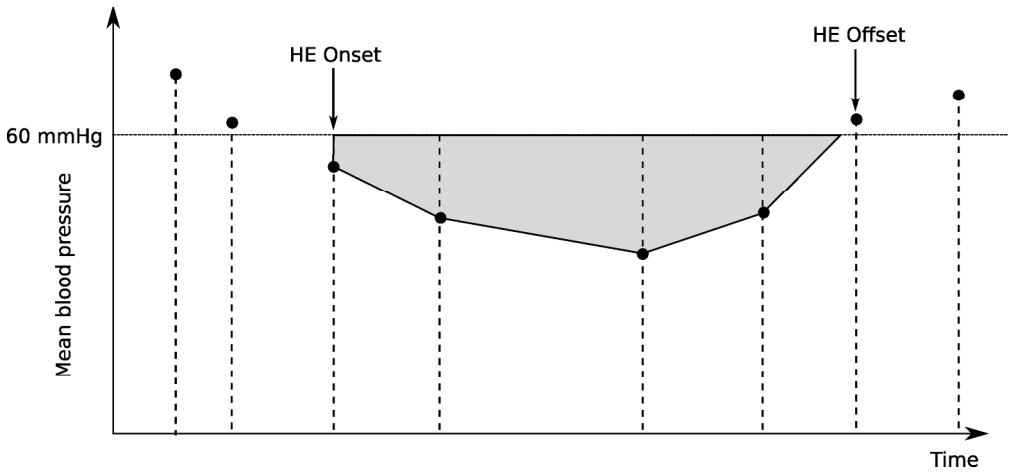

Figure 1: A pictorial illustration of Hypotension Severity Index (HSI) calculation. The grayed area in mmHg·min represents the HSI in this particular case. Consecutive mean blood pressure measurements are linearly interpolated, and the area below 60 mmHg from the first to last measurement of the HE is computed. HSI has the advantage of harnessing both magnitude of mean blood pressure and HE duration.

The authors confirm that the manuscript conforms to the items listed below.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Interrogating a clinical database to study treatment of hypotension in the critically ill

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Interrogating a clinical database to study treatment of hypotension in the critically ill

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Key words: hypotension, vasoactive agents, fluid resuscitation, electronic medical record

Word count: 4,153

Abstract

Objective: In intensive care, it is imperative to resolve hypotensive episodes (HEs) in a timely manner to minimize end-organ damage. Clinical practice guidelines generally recommend initial treatment with fluid resuscitation followed by vasoactive agent administration if patients remain hypotensive. However, the impact of such interventions on patient outcomes has not been clearly established. Hence, the objective of this study was to investigate the relationship between fluid and vasoactive agent interventions and patient outcomes, while highlighting the utility of electronic medical records in clinical research.

Design: Retrospective cohort study.

Setting: Intensive care units (ICUs) at a large, academic, tertiary medical center.

Participants: Patients in MIMIC-II (a large electronic ICU database) who experienced a single HE during their ICU stay. 2,332 patients had complete data.

Primary and secondary outcome measures: The primary outcome of interest was in-hospital mortality. Secondary outcomes were ICU length of stay (LOS), HE duration, Hypotension Severity Index (HSI) (defined as the MAP curve area below 60mmHg during the HE), and rise in serum creatinine.

Results: Fluid resuscitation was associated with significantly shorter ICU LOS among ICU survivors ($p=0.007$). Vasoactive agent administration significantly decreased HE duration ($p<0.001$) and HSI ($p=0.002$) but was associated with increased in-hospital mortality risk ($p<0.001$), prolonged ICU LOS among ICU survivors ($p=0.04$), and rise in serum creatinine ($p=0.002$) after adjustment for confounders. Propensity score analyses as well as sensitivity analyses in treatment-, diagnosis-, and ICU-service-specific sub-populations corroborated the relationship between vasoactive agents and increased in-hospital mortality.

Conclusions: An adverse relationship between vasoactive agents and in-hospital mortality was found in patients with hypotension. This study has implications for the care of critically ill patients with

hypotension but also illustrates the utility of electronic medical records in research when randomized controlled trials are difficult to conduct.

Article Summary

Article focus:

- To investigate the impact of fluid resuscitation and vasoactive therapy on patient outcomes in critically ill patients who experienced a hypotensive episode, using an electronic database
- To emphasize the utility of electronic medical records in clinical research when prospective randomized clinical trial results are absent

Key messages:

- Vasoactive agents were found to be correlated with increased in-hospital mortality risk, even after propensity adjustment.
- Electronic medical records can help answer clinical questions for which clinical trials are challenging to conduct.

Strengths and limitations of this study:

- The adverse relationship between vasoactive agents and in-hospital mortality was carefully established using propensity score and sensitivity analyses.
- The results of this paper are thought-provoking but inconclusive. It is possible that vasoactive agents harm only a specific subset of the critically ill.

Introduction

Electronic medical records (EMRs) that include detailed information on clinical care afford researchers a unique opportunity to evaluate both practice variation and the impact of diagnostic and therapeutic decisions on patient outcomes. When compiled into clinical databases and used for research purposes, they have potential advantages compared to randomized controlled trials (RCT). For example, clinical databases built using EMRs require fewer resources to mobilize for analysis, are capable of including readily-accessible information on large and diverse patient populations, and allow research questions to be answered within a shorter period of time. Their versatility also makes them a potential resource for policymakers, as public and private healthcare payers increasingly rely on clinical evidence to support practice guidelines and coverage decisions. Another advantage associated with EMRs is that they can be used to assess interventions in real-life practice, whereas RCTs tend to focus on arguably artificial clinical scenarios stemming from their strict inclusion and exclusion criteria.

The Multi-parameter Intelligent Monitoring in Intensive Care II (MIMIC-II) database (1) is a clinical database that provides detailed information about the care of patients treated in intensive care units (ICUs). Critically ill patients are an ideal population for clinical database investigations because the clinical value of many treatments and interventions they receive is unproven, and high-quality data supporting or discouraging specific practices is relatively sparse (2,3). We used MIMIC-II to explore practice variation and health outcomes in critically ill patients admitted for or later developing hypotension in an ICU. Hypotension is an important condition to study in this setting because it is a risk factor for hospital mortality and approaches to its treatment vary widely (e.g., colloids vs. crystalloids for fluid resuscitation (4,5)). Moreover, many of the interventions used to treat hypotension are associated with adverse events including pulmonary edema, heart failure, and tissue ischemia (6–9).

Methods

Study Population

This study utilized the MIMIC-II database (version 2.6), a publicly available clinical database developed through a collaboration among Massachusetts Institute of Technology (MIT), Philips Healthcare, and Beth Israel Deaconess Medical Center (BIDMC) (1). MIMIC-II is a repository of de-identified physiologic, laboratory, and survival outcome data from approximately 25,000 critically ill adult patients cared for in the ICUs at BIDMC between 2001 and 2008. These data include clinical variables such as patient age, gender, and chronic disease diagnoses as represented by International Classification of Diseases (ICD) codes; laboratory data such as hematocrit, creatinine, and electrolytes; physiologic data such as blood pressure and heart rate; markers of treatment intensity such as the utilization of invasive and noninvasive mechanical ventilation, renal-replacement therapy, central venous lines, vasoactive agents, and blood transfusion; and survival during and after the hospitalization.

Patients in MIMIC-II who were cared for in medical ICUs (MICU), surgical ICUs (SICU), coronary care units (CCU), and cardiac surgery recovery units (CSRU) were included in the study. In addition, patients were eligible for inclusion in this study if they experienced a single hypotensive episode (HE) and their code status was not comfort-measures-only within 24 hours before and after the HE. Hypotension was defined based on mean arterial pressure (MAP) measurements obtained either by invasive arterial catheters or non-invasive sphygmomanometers. Both types of measurement were usually recorded every 10-15 minutes in our cohort; although invasive arterial catheters yield beat-by-beat blood pressure, we utilized nurse-verified measurements that are still recorded every 10-15 minutes. The beginning of an HE was defined as the time of the first of two consecutive MAP measurements less than or equal to 60 mmHg, preceded by two consecutive MAP values above 60 mmHg. The end of an HE was defined as the time of the first of two consecutive MAP measurements greater than 60 mmHg, preceded by two

consecutive MAP values less than or equal to 60 mmHg. A MAP threshold of 60 mmHg was used in the study based on the finding that autoregulation ceases and blood flow becomes pressure dependent below this level in various organs (10).

Study Variables and Outcomes

The two primary independent variables of interest were administration of intravenous fluid and initiation or increase in dosage of vasoactive agents during the HE. Fluid resuscitation was defined as at least one infusion of either a bolus of isotonic crystalloid of at least 250 ml or any volume of colloids. Vasoactive therapy was defined as an initiation or a dosage increase of dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine, or vasopressin during the HE. Not all patients received fluids or vasoactive agents during their HE.

The primary patient outcome was in-hospital mortality, while the secondary outcomes were ICU length of stay (LOS) longer than 3 days, HE duration longer than 1 hour, Hypotension Severity Index (HSI), defined as the MAP curve area below 60 mmHg during the HE, and any increase in serum creatinine level within three days following the HE. Figure 1 illustrates how we calculated HSI for each HE. HSI approximates the area between linearly interpolated mean blood pressure measurements and the 60 mmHg and captures both HE duration and magnitude of blood pressure in one metric. The unit of HSI is mmHg·min. As an outcome variable, HSI was first calculated as a continuous value and subsequently dichotomized with a threshold of 150 mmHg·min (roughly the median HSI in the cohort). ICU LOS was investigated in all patients, as well as only among the patients who survived their ICU stay.

Control variables in this study included age, gender, Simplified Acute Physiologic Score (SAPS) (a predictor of mortality for critically ill patients), an Elixhauser comorbidity score (11) calculated using the method described by Walraven et al (12) (indicator of chronic illness and secondary diagnoses), mean MAP in the 3-hour period immediately prior to the HE onset (measure of hemodynamic status before the

HE), total volume of urine output in the 3-hour period immediately prior to the HE onset greater than 200 ml (surrogate measure of organ perfusion), last serum creatinine level prior to and within 24 hours of the HE onset (another surrogate measure of organ perfusion), and service type (MICU, SICU, CCU, or CSRU). In addition, all propensity score models in this study (to be discussed in the next section) included the total volume of fluids (normal saline and lactated ringer) given to the patient between ICU admission and the beginning of the HE.

Statistical Analysis

The effects of hypotension treatment approaches on patient outcomes were investigated after adjusting for confounding variables using multivariate logistic regression. For each logistic regression model, the Hosmer-Lemeshow (H-L) goodness-of-fit test (13) and receiver operating characteristic (ROC) curve analysis were performed to evaluate the calibration and discrimination of the model, respectively. For all outcomes, p-values less than 0.05 were considered significant.

In order to further address omitted variable bias in the in-hospital mortality analysis, a propensity score analysis (14) was employed to adjust for the likelihood of receiving vasoactive therapy. A logistic regression model with all control variables was built to estimate propensity scores for receipt of vasoactive therapy, while remaining blind to in-hospital mortality. Propensity scores were then used in a subsequent regression model as a regressor along with the primary predictors (fluids and vasoactive agents), while the outcome variable was in-hospital mortality.

As a sensitivity analysis, in-hospital mortality with and without adjustment using propensity scores was analyzed after excluding patients who received neither fluids nor vasoactive agents during their HE. By focusing only on treated patients, patients with a potentially clinically unimportant HE were excluded. Similarly, in-hospital mortality with and without propensity score adjustment was also investigated within patients who received either only fluids or both fluids and vasoactive agents (in other words, fluid

resuscitated patients, who comprise a subset of the treated patients). By excluding patients who received only vasoactive agents and no fluids during their HE, this sensitivity analysis reduced the number of patients whose clinical presentations were more severe.

In addition, differences across the four service types in the underlying cause of hypotension, and hence in hypotension treatment methods, were addressed by conducting an ICU-service-specific sensitivity analysis. Specifically, a separate propensity score model was built in each service type to investigate in-hospital mortality. We also performed subgroup analyses among patients with sepsis and among patients with congestive heart failure (CHF) based on ICD-9 codes. The rationale was to address potential bias by indication. Separate logistic regression models with propensity score adjustment were constructed for these analyses.

All statistical analyses were performed using MATLAB version R2010b (MathWorks, Natick, MA).

Results

A total of 3,163 patients in MIMIC-II met the inclusion criteria. Of these patients, 63.3% and 81.6% developed an HE within 24 and 48 hours of ICU admission, respectively. Table 1 summarizes the demographic and clinical characteristics of the patients in our cohort. The median HE duration was 2 hours. Most HEs (62.9%) were treated with neither fluids nor vasoactive agents, whereas 19.8% of the patients were fluid resuscitated. The incidence of vasoactive agent use was 17.3% as monotherapy and 6.3% in combination with fluids. The in-hospital mortality of the patient cohort was 12.9%, while the median ICU LOS was 2.7 days. Of the 3,163 patients, 732 and 354 were CHF and sepsis patients, respectively. Also, 1,486 and 1,677 patients were monitored using invasive and non-invasive blood pressure measurement techniques, respectively.

Table 2 summarizes results for in-hospital mortality stratified by treatment. Of the 3,163 patients, 2,332 had complete data and were included in multivariate analyses. The largest contributor to missing data was

serum creatinine. While no significant relationship was found between fluid resuscitation and in-hospital mortality, vasoactive therapy was associated with an increased in-hospital mortality risk in all (odds ratio (OR)=2.86, p<0.001), treated (received either fluids or vasoactive agents, or both) (OR=2.41, p=0.02), and fluid resuscitated patients (received either only fluids or both fluids and vasoactive agents) (OR=2.30, p=0.04). Among the control variables, older age, higher SAPS, higher Elixhauser, higher mean MAP prior to the HE, lower urine output prior to the HE, and MICU (in comparison to SICU, CCU, and CSRU) were significantly associated with higher in-hospital mortality in the overall cohort. Among the treated patients only, higher SAPS, higher Elixhauser, lower urine output prior to the HE, and MICU (in comparison to CSRU) were associated with higher in-hospital mortality. The multivariate analysis of fluid resuscitated patients showed that higher SAPS, higher Elixhauser, lower urine output prior to the HE, and MICU (in comparison to CCU and CSRU) were all associated with an increased risk of death.

In estimating the propensity for vasoactive therapy in the entire patient cohort, younger age, male gender, higher SAPS, higher Elixhauser, lower urine output prior to the HE, and CSRU (in comparison to MICU) were significantly correlated with higher likelihood of receiving vasoactive agents. In the treated patients, higher SAPS, higher Elixhauser, higher serum creatinine prior to the HE, and CSRU (in comparison with MICU) were significant predictors of vasoactive therapy. Among the patients who received fluid resuscitation, higher SAPS, higher serum creatinine prior to the HE, and CSRU (in comparison with MICU) were associated with increased propensity. See Appendix I for detailed results of the propensity score calculation models.

Table 3 summarizes the relationship between vasoactive therapy and in-hospital mortality after propensity score adjustment. Vasoactive therapy remained significantly associated with increased mortality, in all (OR=2.44, p<0.001), treated (OR=2.21, p=0.009), and fluid resuscitated patients (OR=1.03, p=0.02). However, in comparison with our results in Table 2, the corresponding vasoactive agent ORs for in-hospital mortality decreased, most substantially in patients who received fluid resuscitation (from 2.30 to 1.03).

The results from the ICU-service-specific analysis are tabulated in Appendix II. After propensity adjustment, the relationship between vasoactive agents and higher in-hospital mortality remained significant in all service types except CSRU. Fluid resuscitation was not significantly correlated with in-hospital mortality in any service type.

Our subgroup analyses yielded similar findings as the main analyses. In the 732 patients with CHF, vasoactive therapy remained significantly correlated with in-hospital mortality after propensity score adjustment (OR=2.00, p=0.004). Likewise, in the 354 sepsis patients, vasoactive therapy was a significant predictor of in-hospital mortality with (OR=2.84, p<0.001) after propensity score adjustment.

Table 4 provides the multivariate logistic regression results for the secondary outcomes in all patients. We found that fluid resuscitation was significantly associated with shorter ICU LOS (all patients: OR=0.71, p=0.004; ICU survivors: OR=0.71, p=0.007) and greater HSI (OR=1.26, p=0.04). Vasoactive agent administration was significantly associated with longer ICU LOS among ICU survivors (OR=1.29, p=0.04), shorter HE duration (OR=0.29, p<0.001), decreased HSI (OR=0.72, p=0.002), and rise in serum creatinine (OR=1.44, p=0.002).

Discussion

Clinical databases built using EMRs such as MIMIC-II represent an opportunity to study clinical areas where practice variation exists or care standards have not been established. In this study, we examined treatment of hypotension in the ICU. The decision to administer intravenous fluids or vasoactive agents, and the volume or dose chosen, largely depend on the clinician's preferences and practice patterns within an ICU, along with process-related factors at the time of the hypotensive event (e.g., physician presence at the bedside, nurse-to-patient ratio, etc.) (15). Clinician decision-making, in the absence of strong guidelines, is frequently driven by prior experience, which is particularly prevalent in intensive care where RCT evidence is relatively sparse (16,17). This results in significant care variability not explained

by patient or contextual factors but instead driven by individual provider practice. Use of inotropes, for example, has been described as both hospital- and physician-dependent, being administered to as few as 5% or to as many as 100% of patients undergoing elective cardiac surgery (18,19).

In our retrospective analysis, we did not find significant variation in the rate of fluid administration, with majority of the patients receiving between 250 and 500 ml/hr. The limited variability in fluid administration volume may explain why we did not find a relationship between fluid administration and in-hospital mortality or some of our secondary outcomes. The administration of vasoactive agents, however, was an independent predictor of in-hospital mortality, and this relationship persisted in the propensity score analysis. To address the issue of confounding by indication, multivariate logistic regression and propensity score analyses were performed in each service type as well as in subsets of patients with CHF or sepsis. In all of these analyses except in CSRU patients, vasoactive agent use remained independently associated with in-hospital mortality.

Other studies have also reported that vasoactive therapy may be associated with higher mortality. Shahin and colleagues (20) found that hospital mortality and renal dysfunction were consistently lower in patients unexposed to inotropes, even when their six-hour physiologic variables were lower than literature-recommended targets. In patients with heart failure, a systematic review of controlled trials of catecholaminergic agents compared to placebo found no improvement in patient outcomes—indeed, there was evidence of harm (21). Using data from the multi-center trial of L-NMMA in septic shock, Dunser et al (22) found that mean vasoactive agent load was associated with higher 28-day mortality.

Catecholamines have a wide range of potential adverse effects (6), including excess vasoconstriction and impaired microcirculation leading to impaired organ perfusion and increased metabolic demands, including myocardial oxygen requirement. Furthermore, catecholamine use has been associated with reduced metabolic efficiency by promoting fatty acid oxidation. Catecholamines have also been associated with increased bacterial virulence and biofilm formation and altered immune response

(6,23,24).

Clinical guidelines for the management of sepsis (25) and cardiogenic shock (26) recommend fluid resuscitation and vasopressor/inotropic support. However, they also state that the recommendations are based on a low level of evidence. Furthermore, in a review article regarding cardiogenic shock (27), Reynolds and Hochman have suggested that the lowest possible doses should be administered when vasopressor and inotropic agents are used, due to a possible relationship between high doses of vasoactive agents and worse survival outcomes (28).

Clinical databases built using EMRs may be ideal resources for evaluating the impact of vasoactive agents on outcomes. Randomized placebo-controlled clinical trials for commonly used vasoactive agents are either unavailable or lack sufficient statistical power to evaluate differences in important clinical outcomes (25). Our study was not able to address whether the observed increase in hospital mortality was more likely to occur with some vasoactive agents than others due to inadequate power. De Backer et al (29) found no significant difference in 28-day mortality between patients who received dopamine as first-line vasopressor therapy and those who received norepinephrine, although dopamine use was associated with significantly more arrhythmias. In our cohort, there were 76 and 171 patients who received only dopamine and norepinephrine, respectively. The unadjusted in-hospital mortality rates in the dopamine and norepinephrine groups were 39.5% and 32.8%, respectively.

It is important to note that, despite our use of propensity scores, residual confounding remains a concern. We attempted to address this by repeating our analyses in patient subsets but we may not have fully adjusted for severity of illness. Little data elsewhere exist that examine the impact of vasoactive agents on end-organ preservation. This area may be a promising one for clinical trials.

There are a few limitations associated with the present study. First, potential bias stemming from missing data abounds. Of the 3,163 patients who met the inclusion criteria, 2,332 had complete data and were analyzed. Second, the duration and dosage of vasoactive therapy during the HE were not investigated.

The analysis was restricted to the identified HEs; the use of vasoactive agents throughout the ICU stay outside the HE was not evaluated. Third, although we included the total amount of fluids given to the patient prior to the HE in the propensity score models, an assessment of fluid responsiveness was not included in the models. Traditional static measures such as central venous pressure were not consistently obtained among the patients, and have been shown to be poorly predictive of fluid responsiveness (30). Dynamic measures have not been sufficiently standardized and validated across critically ill patients, especially those who are spontaneously breathing, those who are mechanically ventilated but not deeply sedated or those who have cardiac arrhythmias. We made the assumption that vasoactive agents were initiated or their dose increased after clinician assessment that the patient will not benefit from additional fluid administration.

Alternative interpretations of our findings are possible. It may be that the adverse relationship between vasoactive agents and survival actually comprises a combination of incremental benefits in a subset of patients that are outweighed by incremental harms in another subset. The threshold blood pressure below which end-organ damage ensues likely differs among patients, and perhaps even within the same patient in different clinical contexts. The clinical challenge is to predict the lowest blood pressure threshold for which no treatment is required. The concept of permissive hypotension has been introduced in the neonatal intensive care literature based on findings of similar outcomes between normotensive and hypotensive low birth weight infants with signs of good perfusion (31). Permissive hypotension would be challenging to investigate prospectively; however, analyses with robust electronic medical records may hold the key to unraveling this conundrum.

Our study is a first step in examining management of hypotension in the ICU, and it suggests potential areas of investigation and standardization of processes of care. The frequency of vasoactive agent use in the ICU may have engendered a perception of safety. Titration of hemodynamic interventions such as vasoactive therapy using a fixed blood pressure target is straightforward to apply at the bedside and likely perceived as rewarding to the staff. Personalized guidelines that are patient- and context-specific may be

more beneficial, particularly when treatment is associated with significant harm. Robust customization of hypotensive thresholds may be best achieved by utilizing extensive real-time modeling of physiologic variables on a patient-by-patient basis. Prospectively, prediction of outcomes with vasoactive therapy may be sought with the help of growing clinical databases to create treatment algorithms.

In a previous study, Celi et al (32) introduced a method of designing decision support tools based on a hospital's own clinical database as an alternative to expert systems derived from large, multi-center, interventional or observational studies. Using the term "Collective Experience" to refer to the aggregation of patient care data from clinicians working in a single institution, they proposed developing guideline models from a more homogeneous group of patients because of the tradeoff between generalizability and accuracy. The utility of a local EMR in clinical decision support when the existing literature lacks relevant evidence was also discussed by Frankovich et al (33). Clinical guidelines developed by a single institution may provide diagnostic assistance, treatment guidance, and prognostic capabilities that are more personalized and appropriate for an institution's patient population. The vision is a data-fueled learning system that aggregates and analyzes day-to-day experimentations, where new knowledge is constantly extracted and propagated for quality improvement, and where practice is driven by outcomes, and less so by individual clinician knowledge base and experience and the local medical culture.

Conclusions

Using an EMR, we found that patients who were exposed to vasoactive therapy during hypotensive episodes were more likely to die, a finding consistent with other studies in sepsis, cardiac surgery, and heart failure. Clinical databases such as MIMIC-II can complement knowledge gained from conventional comparative-effectiveness research methods and provide important insights about routine patient care.

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Competing Interests

All authors declare that there is no competing interest associated with this research.

Data Sharing

There is no additional data available. This study was conducted based on the public MIMIC-II database. Any interested researcher can gain access to MIMIC-II; for details, please see http://physionet.org/mimic2/.

Contributors

JL designed the study, conducted data extraction and analyses, and wrote most parts of the manuscript. RK designed the study, helped with data extraction, and critically revised the manuscript. JAL wrote the discussion section and critically revised the manuscript. DJS helped with data extraction and critically revised the manuscript. LAC designed the study, wrote the discussion section, and critically revised the manuscript. JL and LAC are the guarantors of the study. All authors had full access to all of the data.

Figure Captions

Figure 1: A pictorial illustration of Hypotension Severity Index (HSI) calculation. The grayed

area in mmHg·min represents the HSI in this particular case. Consecutive mean blood pressure measurements are linearly interpolated, and the area below 60 mmHg from the first to last measurement of the HE is computed. HSI has the advantage of harnessing both magnitude of mean blood pressure and HE duration.

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Table 1: Demographic and clinical characteristics of the study population (N=3163).

Age* (yr)		69.3 [56.9,79.3]
Gender (male)		54.3%
Service type		
	MICU	33.2%
	SICU	22.0%
	CCU	15.8%
	CSRU	29.0%
SAPS I*		15 [11,19]
HE duration* (min)		120 [45,120]
Hypotension treatment		
	No intervention	62.9%
	Fluids only	13.5%
	Vasoactive agents only	17.3%
	Both fluids and vasoactive agents	6.3%
In-hospital mortality		12.9%
ICU LOS* (days)		2.7 [1.6,4.9]
Elixhauser comorbidities		
	Congestive heart failure	20.9%
	Cardiac arrhythmias	21.0%

Valvular disease	8.6%
Pulmonary circulation disorders	2.4%
Peripheral vascular disorders	9.5%
Hypertension	30.9%
Paralysis	1.1%
Other neurological disorders	3.3%
Chronic pulmonary disease	16.4%
Diabetes, uncomplicated	21.2%
Diabetes, complicated	4.8%
Hypothyroidism	8.7%
Renal failure	5.1%
Liver disease	4.6%
Peptic ulcer disease excluding bleeding	0.5%
AIDS	0.6%
Lymphoma	1.5%
Metastatic cancer	4.4%
Solid tumor without metastasis	10.8%
Rheumatoid arthritis/collagen vascular disease	2.2%
Coagulopathy	6.1%
Obesity	1.6%
Weight loss	2.7%

Fluid and electrolyte disorders	24.3%
Blood loss anemia	0%
Deficiency anemias	11.9%
Alcohol abuse	3.7%
Drug abuse	1.8%
Psychoses	2.3%
Depression	4.1%

* median [Q_1,Q_3]

MICU: medical intensive care unit, SICU: surgical intensive care unit, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, LOS: length of stay, HE: hypotensive episode

Table 2: Multivariate logistic regression results for in-hospital mortality, shown in odds ratio (95% CI). Each column represents a separate regression model for a specific patient cohort. Treated patients received either fluids or vasoactive agents, or both. Fluid resuscitated patients received either only fluids or both fluids and vasoactive agents.

	All patients	Treated patients	Fluid resuscitated patients
Fluid resuscitation	0.87 (0.61-1.26)	0.75 (0.40-1.40)	N/A
Use of vasoactive agents	2.86* (2.09-3.92)	2.41* (1.19-4.88)	2.30* (1.05-5.03)
Age (yr)	1.01* (1.00-1.02)	1.01 (0.99-1.02)	1.02 (1.00-1.05)
Gender (male)	0.96 (0.72-1.27)	0.93 (0.59-1.47)	0.82 (0.40-1.67)
SAPS	1.14* (1.11-1.18)	1.17* (1.12-1.22)	1.18* (1.10-1.27)
Elixhauser	1.24* (1.14-1.36)	1.15* (1.01-1.32)	2.00* (1.26-3.17)
Mean MAP prior to HE (mmHg)	1.02* (1.00-1.03)	1.02 (1.00-1.04)	1.02 (0.99-1.06)
Urine output prior to HE > 200ml	0.65* (0.49-0.87)	0.57* (0.35-0.91)	0.30* (0.13-0.68)
Creatinine prior to HE (mg/dl)	1.07 (0.96-1.19)	1.07 (0.90-1.28)	1.05 (0.75-1.49)
Service type			
MICU**	1	1	1
SICU	0.62* (0.43-0.88)	0.62 (0.35-1.08)	0.37* (0.15-0.91)
CCU	0.63* (0.42-0.94)	0.61 (0.32-1.14)	0.25* (0.07-0.86)
CSRU	0.08* (0.05-0.14)	0.05* (0.02-0.11)	0.14* (0.05-0.41)
Number of subjects	2332	812	409

	All patients	Treated patients	Fluid resuscitated patients
AUC	0.831	0.868	0.877
Hosmer-Lemeshow p-value	0.37	0.40	0.86

* Statistically significant

** Reference

CI: confidence interval, SAPS: Simplified Acute Physiology Score, MAP: mean arterial pressure, HE: hypotensive episode, MICU: medical intensive care unit, SICU: surgical intensive care unit, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, AUC: area under the receiver operating characteristic curve, N/A: not applicable

Table 3: Vasoactive therapy propensity score analysis results for in-hospital mortality, shown in odds ratio (95% CI). Each column represents a separate regression model for a specific patient cohort. Treated patients received either fluids or vasoactive agents, or both. Fluid resuscitated patients received either only fluids or both fluids and vasoactive agents.

	All patients	Treated patients	Fluid resuscitated patients
Fluid resuscitation	0.97 (0.70-1.33)	0.87 (0.54-1.41)	N/A
Use of vasoactive agents	2.44* (1.85-3.20)	2.21* (1.22-4.01)	1.03* (1.00-1.05)
Propensity for vasoactive therapy	2.03 (0.83-5.00)	0.96 (0.28-3.24)	5.41* (1.12-26.26)
Number of subjects	2332	812	409
AUC	0.621	0.602	0.629
Hosmer-Lemeshow p-value	0.01	0.02	0.03

* Statistically significant

AUC: area under the receiver operating characteristic curve, N/A: not applicable

Table 4: Multivariate regression results for the secondary outcomes in all patients, shown in odds ratio (95% CI). Each column represents a separate regression model for each secondary outcome variable.

	ICU LOS > 3 days (all patients)	ICU LOS > 3 days (ICU survivors only)	HE duration > 1 hr	HSI > 150 mmHg·min	Rise in serum creatinine
Fluid resuscitation	0.71* (0.57-0.90)	0.71* (0.55-0.91)	0.89 (0.70-1.14)	1.26* (1.01-1.57)	1.14 (0.90-1.45)
Use of vasoactive agents	1.05 (0.84-1.30)	1.29* (1.01-1.65)	0.29* (0.23-0.36)	0.72* (0.59-0.89)	1.44* (1.15-1.80)
Age (yr)	1.00 (0.99-1.00)	0.99* (0.99-1.00)	1.00 (1.00-1.01)	1.01* (1.00-1.01)	1.01 (1.00-1.01)
Gender (male)	0.96 (0.81-1.15)	0.99 (0.81-1.20)	0.83 (0.69-1.01)	0.85 (0.71-1.01)	1.07 (0.88-1.29)
SAPS	1.07* (1.05-1.09)	1.13* (1.10-1.15)	0.96* (0.94-0.98)	0.99 (0.97-1.01)	1.02* (1.00-1.04)
Elixhauser	1.24* (1.18-1.30)	1.23* (1.17-1.29)	1.19 (0.95-1.48)	1.13 (1.00-1.27)	2.14* (1.30-3.52)
Mean MAP prior to HE (mmHg)	1.03* (1.02-1.04)	1.04* (1.03-1.05)	0.95* (0.94-0.96)	0.98* (0.97-0.99)	1.00 (0.99-1.01)
Urine output prior to	0.73* (0.61-	0.76* (0.63-	1.29* (1.06-	1.10 (0.92-	0.75* (0.62-

	ICU LOS > 3 days (all patients)	ICU LOS > 3 days (ICU survivors only)	HE duration > 1 hr	HSI > 150 mmHg·min	Rise in serum creatinine
HE > 200ml	0.87)	0.92)	1.56)	1.30)	0.90)
Creatinine prior to HE (mg/dl)	1.01 (0.93-1.09)	1.05 (0.95-1.15)	0.98 (0.90-1.07)	0.99 (0.92-1.08)	1.01 (0.92-1.11)
Service type					
MICU**	1	1	1	1	1
SICU	1.61* (1.26-2.07)	1.62* (1.23-2.13)	0.77 (0.59-1.01)	0.76* (0.60-0.97)	1.00 (0.78-1.29)
CCU	1.20 (0.91-1.58)	1.34 (0.99-1.81)	0.70* (0.52-0.94)	0.78 (0.60-1.02)	1.23 (0.93-1.63)
CSRU	0.77* (0.60-0.98)	0.58* (0.44-0.76)	0.65* (0.50-0.84)	0.58* (0.46-0.74)	1.99* (1.55-2.56)
Number of subjects	2332	2114	2332	2332	1989
AUC	0.692	0.721	0.733	0.624	0.635
Hosmer-Lemeshow p-value	0.22	0.42	0.02	0.16	0.69

* Statistically significant

** Reference

CI: confidence interval, SAPS: Simplified Acute Physiology Score, MAP: mean arterial pressure, HE: hypotensive episode, ICU: intensive care unit, MICU: medical ICU, SICU: surgical ICU, CCU: coronary care unit, CSRU:

cardiac surgery recovery unit, LOS: length of stay, AUC: area under the receiver operating characteristic curve

Appendix I

The table below summarizes the relationships between demographic/clinical variables and the propensity for receipt of vasoactive therapy, shown in odds ratio (95% CI). Each column represents a separate propensity score model for a specific patient cohort. Treated patients received either fluids or vasoactive agents, or both. Fluid resuscitated patients received either only fluids or both fluids and vasoactive agents.

	All patients	Treated patients	Fluid resuscitated patients
Age (yr)	0.99* (0.99-1.00)	0.99 (0.98-1.01)	0.99 (0.98-1.01)
Gender (male)	1.55* (1.25-1.92)	1.21 (0.87-1.67)	1.34 (0.83-2.18)
SAPS	1.12* (1.09-1.14)	1.09* (1.06-1.13)	1.12* (1.07-1.17)
Elixhauser	1.08* (1.01-1.17)	1.30* (1.03-1.64)	N/A
Mean MAP prior to HE (mmHg)	1.01 (0.99-1.02)	1.01 (0.99-1.03)	1.00 (0.98-1.03)
Urine output prior to HE > 200ml	0.71* (0.57-0.88)	0.85 (0.61-1.18)	0.98 (0.60-1.59)
Creatinine prior to HE (mg/dl)	1.01 (0.92-1.11)	1.28* (1.07-1.52)	1.29* (1.02-1.64)
Total volume of fluids given prior to HE (L)	1.01 (0.97-1.05)	1.01 (0.96-1.07)	0.97 (0.89-1.05)
Service type			
MICU**	1	1	1
SICU	0.74 (0.53-1.03)	0.95 (0.60-1.50)	1.28 (0.64-2.56)
CCU	1.37 (0.97-1.94)	1.68 (1.00-2.84)	1.41 (0.59-3.37)
CSRU	2.06* (1.55-2.75)	2.84* (1.87-4.32)	3.56* (1.91-6.62)

	All patients	Treated patients	Fluid resuscitated patients
Number of subjects	2332	812	409
AUC	0.726	0.703	0.729
Hosmer-Lemeshow p-value	0.03	0.17	0.16

* Statistically significant

** Reference

CI: confidence interval, SAPS: Simplified Acute Physiology Score, MAP: mean arterial pressure, HE: hypotensive episode, MICU: medical intensive care unit, SICU: surgical intensive care unit, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, AUC: area under the receiver operating characteristic curve, N/A: not applicable (due to a lack of significant relationship with receipt of vasoactive therapy)

Appendix II

The table below summarizes the relationships between demographic/clinical variables and the propensity for receipt of vasoactive therapy in different service types, shown in odds ratio (95% CI). Each column represents a separate propensity score model for a specific service type.

	MICU	SICU	CCU	CSRU
Age (yr)	0.99 (0.98-1.00)	0.99 (0.98-1.01)	0.99 (0.96-1.01)	1.00 (0.99-1.01)
Gender (male)	1.86* (1.20-2.87)	1.45 (0.84-2.49)	1.50 (0.84-2.69)	1.60* (1.14-2.24)
SAPS	1.16* (1.11-1.21)	1.15* (1.09-1.21)	1.15* (1.09-1.21)	1.04* (1.00-1.09)
Elixhauser	1.04 (0.91-1.20)	1.09 (0.93-1.29)	1.23* (1.02-1.49)	1.05 (0.93-1.18)
Mean MAP prior to HE (mmHg)	1.00 (0.98-1.03)	1.01 (0.99-1.04)	1.03 (1.00-1.06)	0.99 (0.97-1.01)
Urine output prior to HE > 200ml	0.57* (0.36-0.92)	0.50* (0.29-0.86)	1.29 (0.74-2.25)	0.72* (0.52-1.00)
Creatinine prior to HE (mg/dl)	1.10 (0.96-1.27)	1.10 (0.90-1.35)	1.09 (0.88-1.36)	0.57* (0.40-0.79)
Total volume of fluids given prior to HE (L)	1.03 (0.95-1.13)	1.02 (0.92-1.14)	0.99 (0.89-1.11)	1.00 (0.94-1.07)
Number of subjects	692	535	379	726
AUC	0.751	0.748	0.740	0.603
Hosmer-Lemeshow	0.71	0.01	0.93	0.33

	MICU	SICU	CCU	CSRU
p-value				

* Statistically significant

CI: confidence interval, SAPS: Simplified Acute Physiology Score, MAP: mean arterial pressure, HE: hypotensive episode, MICU: medical intensive care unit, SICU: surgical intensive care unit, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, AUC: area under the receiver operating characteristic curve

The table below shows the vasoactive therapy propensity score analysis results for in-hospital mortality in different service types, shown in odds ratio (95% CI). Each column represents a separate regression model for a specific service type. The propensity for vasoactive therapy was calculated by the models shown in the table above.

	MICU	SICU	CCU	CSRU
Fluid resuscitation	1.02 (0.62-1.69)	0.64 (0.30-1.37)	0.52 (0.17-1.61)	2.14 (0.84-5.46)
Use of vasoactive agents	2.90* (1.82-4.61)	4.53* (2.46-8.34)	3.20* (1.58-6.48)	0.71 (0.27-1.89)
Propensity for vasoactive therapy	70.20* (17.86-275.94)	147.57* (19.39-1122.96)	186.24* (24.41-1420.79)	0.00* (0.00-0.43)
Number of subjects	692	535	379	726
AUC	0.729	0.751	0.791	0.645
Hosmer-Lemeshow p-value	0.29	0.02	0.33	0.37

* Statistically significant

CI: confidence interval, MICU: medical intensive care unit, SICU: surgical intensive care unit, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, AUC: area under the receiver operating characteristic curve

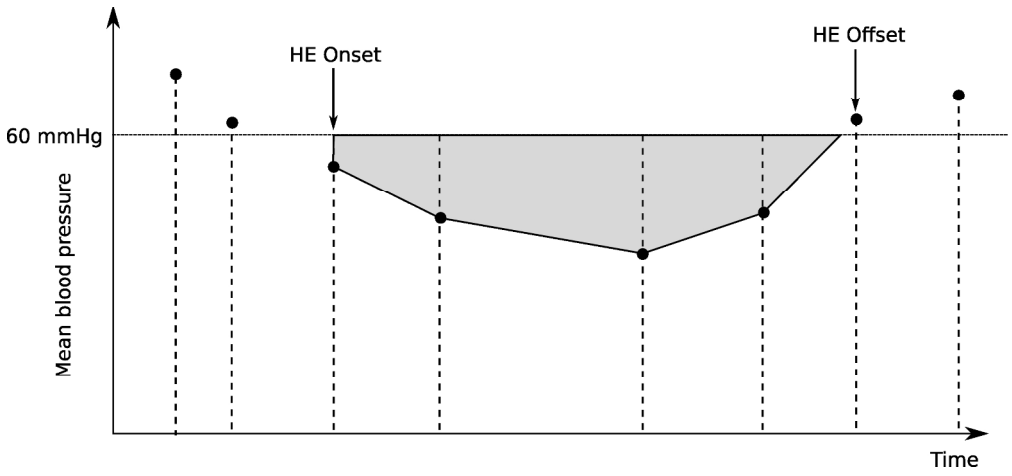

Figure 1: A pictorial illustration of Hypotension Severity Index (HSI) calculation. The grayed area in mmHg·min represents the HSI in this particular case. Consecutive mean blood pressure measurements are linearly interpolated, and the area below 60 mmHg from the first to last measurement of the HE is computed. HSI has the advantage of harnessing both magnitude of mean blood pressure and HE duration.

The authors confirm that the manuscript conforms to the items listed below.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.