2013

Determining predictors of underlying etiology and clinical deterioration in patients with physiologic instability in the emergency department

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

DETERMINING PREDICTORS OF UNDERLYING ETIOLOGY AND CLINICAL DETERIORATION IN PATIENTS WITH PHYSIOLOGIC INSTABILITY IN THE EMERGENCY DEPARTMENT

by

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B.S., University of Michigan, 2009

Submitted in partial fulfillment of the

requirements for the degree of

Master of Arts

2013

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ABSTRACT

Shock is a critical state defined by inadequate oxygen delivery to tissues. It is well known in the critical care community that early diagnosis and treatment of shock are crucial to improving patient outcomes. However, in many cases, when a state of circulatory shock has been reached, irreversible damage already occurred. In the present study, we broadened our patient cohort from those with shock to those with physiologic instability with the intent of finding predictive factors that allow us to recognize when a patient is at risk for deterioration or when it is already occurring. These patients included patients with pre-shock, shock, and other forms of dysfunction. The purpose of this study was to determine the predictors of underlying etiology of physiologic instability as well as the likelihood of clinical deterioration in these various states, using elements from the physical exam, history, laboratory values, and vital sign measurements.

This study was a prospective observational study of patients, from November 15, 2012 to March 1, 2013, found to have physiologic instability in the

emergency department at an urban, academic tertiary-care hospital with 55,000 annual visits. Physiologic instability was defined as any one of the following abnormalities: heart rate (HR) > 130, respiratory rate (RR>24), shock index (SI) > 1, systolic blood pressure (SBP) < 90 mm/hg, and Lactate > 4.0 mmol/L, for a time period of more than five minutes. We identified 540 patients, 74.8% of which were included. Data describing epidemiology, and elements from the patient history and physical exam were abstracted from physician charts and the final etiology of physiologic instability, defined as septic, cardiogenic, hypovolemic, hemorrhagic, or other, was adjudicated by a physician. Blood samples from a subset of our patient group were collected from the hospital hematology laboratory and sent to the Wyss Institute to be analyzed using a novel bacterial detection assay. All of the covariates that data was collected for were analyzed to determine their diagnostic and prognostic value.

The covariates that showed significant predictive value for septic etiology after multivariable analysis were: fever, cough, cellulitis, elevated WBC count, and a past medical history of HIV/AIDS. The Wyss assay, which used Mannose-binding lectin (MBL) attached to beads to detect the presence of bacteria in blood, predicted septic etiology with 45.5% sensitivity and 54.2% specificity. The covariates that were significantly associated with hypovolemic etiology in the multivariable analysis were: nausea/vomiting, diarrhea, and a medical history of myocardial infarction. Cough was negatively associated with hypovolemic etiology in the multivariable analysis. The covariates that were significantly

associated with hemorrhagic etiology were: non-GI bleeding, and a rectal exam finding of either bright red blood or melena. Finally, the covariates with significant predictive value for cardiogenic etiology after multivariable analysis were a medical history of congestive heart failure, shortness of breath, and lower extremity edema. Univariate predictors were also analyzed and discussed for etiology of physiologic instability.

The percentage of patients in each category that showed deterioration were as follows: cardiogenic (6.1%), hypovolemic (11.1%), hemorrhagic (11.5%), and septic (14.9%). The covariates that showed significant positive predictive value for deterioration after multivariable analysis were: hypotension (SBP < 90mmHg), elevated lactate values, and a past medical history of cancer. Univariate predictors were also analyzed and discussed for clinical deterioration, which included cause of physiologic instability as well as covariates from the medical history and physical exam.

The purpose of this study was to characterize physiologic instability in the emergency department and by finding ways predict its underlying etiology and clinical deterioration. We concluded that various elements from the physical exam, patient history, and the Wyss Institute's novel infection diagnostic assay may be useful as efficient predictors of the cause and prognosis of physiologic instability in Emergency Department patients.

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ABBREVIATIONS

BIDMC	Beth Israel Deaconess Medical Center
CAD	Coronary Artery Disease
CHF	Chronic Heart Failure
COPD	Chronic Obstructive Pulmonary Disorder
CRP	C - Reactive Protein
DAMPS	Damage Associated Molecular Patterns
ED	Emergency Department
ESRD	End Stage Renal Disease
HR	Heart Rate
ICAM-1	Intercellular Adhesion Molecule
ICU	Intensive Care Unit
IRB	Institutional Review Board
MI	Myocardial Infarction
MODS	Multiple Organ Dysfunction Syndrome
NICOM	Non Invasive Cardiac Output Monitoring
NPV	Negative Predictive Value
PAI-1	Plasminogen Activation Inhibitor
PAMPS	Pathogen Associated Molecular Patterns
PVD	Peripheral Vascular Disease
SBP	Systolic Blood Pressure

sFLT-1	Soluble Fms-like Tyrosine Kinase-1 Receptor
SI	Shock Index
SIRS	Systemic Inflammatory Response Syndrome
SVT	Supra-ventricular Tachycardia
TLR	Toll Like Receptor
VCAM-1	Vascular Cell Adhesion Molecule
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell

INTRODUCTION

Circulatory shock is a critical state caused when the balance between oxygen supply and demand is severely disrupted, resulting in tissue hypoxia and damage (1). Clinically, it is defined as hypotension that persists even after substantial fluid resuscitation (2). Shock can occur via multiple mechanisms, but without early diagnosis and treatment can possibly lead to organ failure and death (1). It is well defined in the literature that early diagnosis and treatment of shock leads to better outcomes (3). Because early recognition and treatment of shock states lead to optimal outcomes in patients, it is beneficial to recognize the warning signs that occur before the irreversible stages of shock where significant tissue damage and organ failure occur.

Patients will often manifest various signs of physiologic instability (such as abnormal vital signs and blood labs) before deteriorating to an overt shock state (1, 3, 7). Moreover, a large number of patients that ultimately develop shock physiology likely may be identified by physiologic instability. One study showed that even a single episode of hypotension (Systolic Blood Pressure <100) in a pre-hospital or Emergency Department setting increased the risk of death during hospital admission (3), independent of shock state (4). Another study by Berger et. al. showed that patients with a Shock Index value, defined as heart rate divided by systolic blood pressure, with a value of 0.7 or greater were three times more likely to develop hypotension than patients with normal Shock Index values

of approximately 0.5 (5). Furthermore, this group showed determined that the negative predictive value (NPV) of shock index is equal to the NPV of Systemic Inflammatory Response Syndrome (SIRS), or 95%. SIRS criteria are used to diagnose septic shock (6). Additionally, increasing lactate levels are associated with a “stepwise increase in mortality” (4). Moreover, tachycardia and tachypnea are also well known as early signs of compensated shock stages that occur before irreversible stages of shock are reached (7). These vital sign abnormalities occur as compensatory mechanisms activated by the sympathetic response to low oxygen delivery to tissues (3). Tachypnea is a mechanism to increase blood oxygen levels and make up for the initial insult that lowered it, while tachycardia is a response mechanism with the goal of increasing blood delivery to major organs. Tachypnea and increased ventilation are also compensatory mechanisms when a patient becomes acidotic - the body increases respiration during attempts to balance acidotic state (7). Even individually, hypotension, a high shock index, tachypnea, tachycardia and lactic acidosis have correlated with negative outcomes, highlighting the point that even if patients have not reached the critical and sometimes irreversible state of shock, their physiologic instability, defined by abnormal vital signs and lab values, is a strong predictor of their clinical deterioration.

In the present study, we aim to improve the clinical approach to differentiating the etiology of illness for patients with physiologic instability in the Emergency Department. We define physiologic instability or “pre-shock” as

having at least one of the following criteria: tachycardia (HR>130 beats per minute), tachypnea (RR>24 breaths per minute), a Shock Index of greater than 1, or blood lactate levels of greater than 4mmol/L, for a time period of more than five minutes. We define “shock” as systolic blood pressure < 90 mmHg. By developing better ways to diagnose the causes of physiologic instability and exposing elements that predict clinical deterioration in this patient population, which includes pre-shock, shock and other forms of physiologic dysfunction, we will be able to define, recognize, and therefore treat this population more effectively in the emergency department. One of the major benefits of characterizing physiologic instability is that it will give us the opportunity to discover factors that lead to deterioration in patients that are not yet in a critically ill state. In addition, we can isolate predictors of the underlying causes of physiologic Instability, which will result in more rapid treatment of these patients.

Since there is not a significant body of literature that evaluates physiologic instability in the emergency department, and shock patients are a subset of patients with physiologic instability, it is beneficial to look to the multitude of research on the various shock states to provide insight to the causes and outcomes of hemodynamic instability. Shock is one of the most critical forms of physiologic instability and, depending on it underlying etiology, can have a mortality rate of anywhere between 20-50% (3). Because of the high morbidity and mortality associated with shock there are a number of prior initiatives focused on the diagnosis and treatment of shock. In particular, early diagnosis

and treatment is proposed as the best weapon against shock mortality. For instance, Rivers et. al. showed that goal directed therapy initiated in the first six hours of presentation in the Emergency Department improved absolute mortality by 16% (3). Furthermore, the time to intervention and mortality have been shown to decrease synergistically (8). Though early intervention in patients with shock is ideal, it is unfortunately very challenging to implement because of the difficulty of distinguishing between the various etiologies of shock. Because early treatment can decrease the likelihood of death in shock patients, it is not only important to recognize predictors of underlying etiology of shock states, but also predictors of deterioration in patents that are not yet critically ill. Analyzing a broader patient cohort with physiologic instability, as we have done in the present study, will allow us to address both of these issues.

Moreover, it is important to be able to diagnose the underlying etiology of shock efficiently so that it can be treated before irreversible organ damage occurs. There are many causes of shock, which can be grouped by underlying physiology: cardiogenic, septic, hypovolemic, anaphylactic, and neurogenic shock (1, 7, 12, 19). Cardiogenic shock is a state of hypoperfusion caused by cardiac failure leading to persistent hypotension and a substantial decrease in cardiac index, often with adequate or elevating filling pressure (9). Septic shock is defined by the American College of Chest Physicians/Society for Critical Care Medicine Consensus to be a “suspected infection and hypotension (SBP<90mmHg), which persists after a crystalloid infusion of 20-30 cc/kg” (6).

Hypovolemic shock is a reduction in circulating volume caused by dehydration or hemorrhage, leading to a reduction in cardiac output and poor tissue perfusion (1). Anaphylactic shock is an allergic state characterized by profound vasodilation due to release of vasoactive mast cell mediators (1). Neurogenic shock is caused by damage to the spinal cord that interferes with communication from the sympathetic nervous system to the cardiovascular system, causing peripheral vasoconstriction, decreased venous return and thus, reduced cardiac output (1). For the present study we assumed that a majority of our patient cohort would be in shock, or pre-shock, so we used the same categories that are commonly used as etiologies of shock as well as add an additional “other” category.

Even though the underlying etiologies of shock are caused by vastly different mechanisms, they also display significant overlap. For example, both septic shock and cardiogenic shock have an inflammatory component (11). Inflammatory cytokines, IL-1B, IL-6, IL-8, TNF-a, CRP, and soluble adhesion molecules are released during cardiogenic shock (11). Systemic Inflammatory Response Syndrome (SIRS), characteristic of septic shock, can also be caused by poor myocardial perfusion in cardiogenic shock (11). Moreover, impaired perfusion of the intestinal tract could lead to transmigration of bacteria and infection in cardiogenic shock (11). In addition, in hemorrhagic hypovolemic shock, extensive ischemia and reperfusion injury can lead to “Multiple Organ Dysfunction Syndrome” (MODS), which shares a lot of features in common with

SIRS, a component of septic shock, through a similar activation of Toll Like Receptors (TLRs) and initiation of inflammation (10). These various causes of shock have very different mechanisms, and though a lot of their therapies overlap, many of them differ. For example, septic shock needs to be treated with antibiotics, and the other causes of shock do not because they do not include infection (1). Intravenous fluids are used to treat most types of shock, however in cardiogenic shock they can sometimes be harmful, leading to pulmonary edema and heart failure (12). Since many of the causes of physiologic instability are the same as the causes of shock, it is safe to assume that there is a similar overlap between the various etiologies of physiologic instability. Consequentially, the various etiologies of physiologic instability will also require different treatment methods (1, 12).

Since early treatment of shock improves outcome and treatment modality depends on the cause of shock (1, 12), it is logical to infer that outcome depends on the early and accurate diagnosis of the etiology of shock. Thus, we have a conundrum. The causes of the hemodynamic instability in shock are both distinct and overlapping, making them difficult to differentiate yet determining the cause of shock accurately and efficiently is imperative to rapid treatment and optimal patient outcomes. This overlap can be expanded to the broader category of physiologic instability, as abnormal vital signs and lab values may have many overlapping yet distinct causes.

Our study aimed to characterize the patients with physiologic instability, including determining predictors of both its underlying etiology and clinical deterioration. We have expanded the category of shock to physiologic instability, because it will allow us to analyze a larger cohort of patients in order to discover early diagnostic and prognostic markers for shock, pre-shock, and other physiologic dysfunction. We analyzed elements that are easily accessible to physicians in the emergency department early in the patients' visit, including elements from history, physical exam, vital signs, and traditional labs. We also investigated novel biomarkers, in order to look for strong prognostic or diagnostic indicators for patients with hemodynamic instability. We then used these elements to predict underlying etiology of undifferentiated physiologic instability (cardiogenic, septic, hypovolemic, anaphylactic, neurogenic, or other) as well as predict the likelihood of deterioration and mortality in these patients.

Numerous studies have demonstrated the importance of the physical exam and medical history in diagnosing various states of dysfunction. Using elements from the physical exam and history is crucial to early and accurate diagnosis of physiologic instability, because it is some of the first information that a physician has about a patient. Many times a patient's medical history alludes to damage or dysfunction that may predispose them to a particular type of shock or to shock in general (18). Elements of the physical exam, including palpated capillary refill, pulse volume, skin temperature, jugular venous distention and lung exam have been described as useful in diagnosing the underlying etiology of

shock (19). Furthermore, there are numerous additional physical exam symptoms used to ascertain of the severity of shock, which are described in the table below:

Physical Exam Findings and Shock Severity

Box. 1
Signs of shock

Early signs[a]

- Tachypnea
- Tachycardia
- Weak or bounding peripheral pulses
- Delayed capillary refill (>2 seconds)
- Pale or cool skin
- Narrowed pulse pressure
- Oliguria
- Lactic acidosis
- Elevated base deficit

Late signs

- Decreased mental status
- Weak or absent central pulses
- Central cyanosis
- Hypotension
- Bradycardia

[a] Early signs of shock are frequently seen in later stages and late signs such as altered mental status may present early depending on the cause and the patient.

Figure 1: Figure taken from Strehlow, 2010. Early and late symptoms of shock (3).

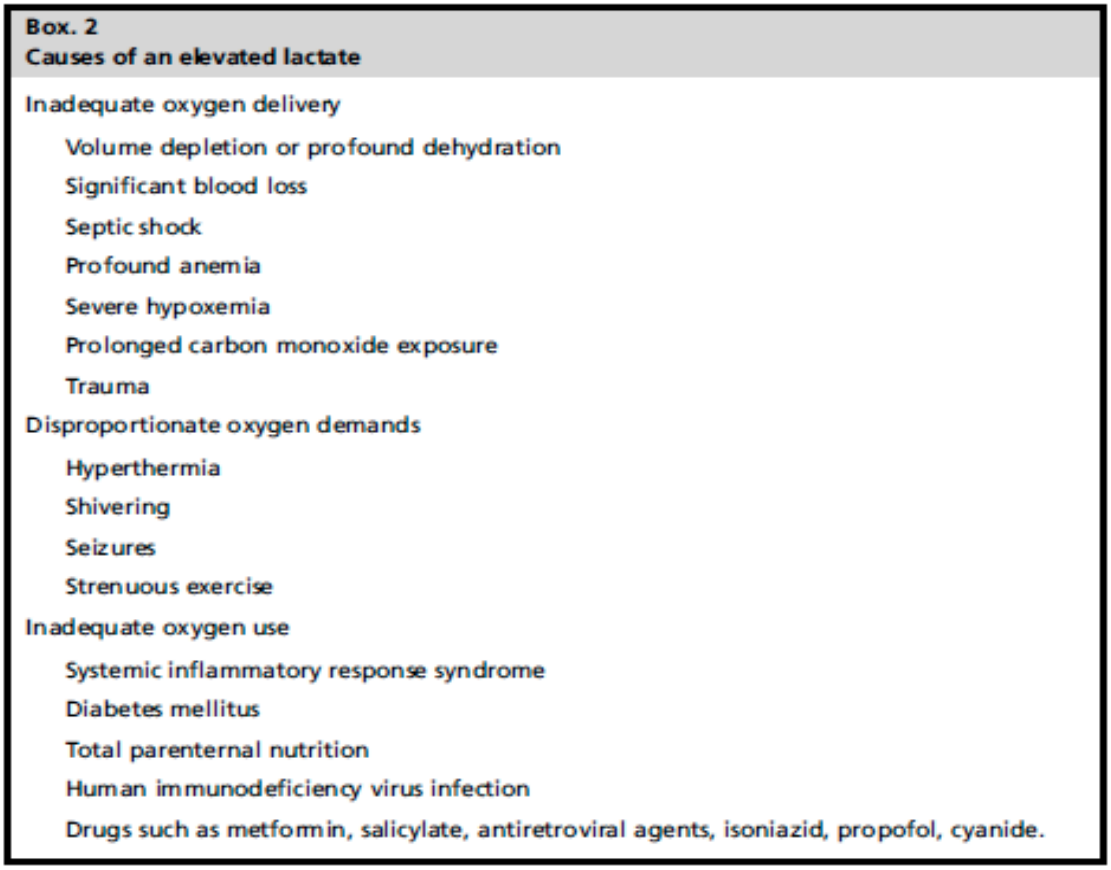
However, there is also research that contrasts these findings and discusses the inaccuracy of ED diagnosis of hemodynamic instability using elements from the history and physical exam. A study by the Nowak group finds that emergency physicians need objective measures of hemodynamic profiles to accurately diagnose acutely ill patients (16). However, this study did not

investigate the predictive value of individual elements in the diagnosis of hemodynamic instability, and it used a very small study cohort of forty patients. In the present study, we aim to determine the diagnostic and prognostic value of specific elements of patient history and physical exam in physiologic instability with a larger cohort of approximately five - hundred patients.

In addition, both vital sign and traditional lab abnormalities may not only alert us of the presence of physiologic instability, but also give us insight into its causes and assist in predicting its outcome. One group discusses the benefits of using basic physiological reasoning to diagnose and manage hemodynamic instability, because of the basic underlying premise that hemodynamic instability is characterized by well-known physiological perturbations (13). This basic physiological reasoning, avoids the less efficient “hit or miss” approach typically employed in diagnosing hemodynamic dysfunction in the emergency department, and saves patients from unnecessary testing and radiology studies (13).

As previously discussed, vital sign abnormalities including: Hypotension, tachycardia, tachypnea can be symptoms of critical illness or warning signs for deterioration. In addition, traditional lab abnormalities may also have some diagnostic and prognostic value in evaluating physiologic instability. Lactic acidosis predicts mortality in various disease states (4). Elevated lactate is a marker of anaerobic metabolism due to inadequate oxygen delivery (3). The table below describes the various causes of lactic acidosis:

Various Causes of Lactic Acidosis



Box. 2
Causes of an elevated lactate

Inadequate oxygen delivery
- Volume depletion or profound dehydration
- Significant blood loss
- Septic shock
- Profound anemia
- Severe hypoxemia
- Prolonged carbon monoxide exposure
- Trauma

Disproportionate oxygen demands
- Hyperthermia
- Shivering
- Seizures
- Strenuous exercise

Inadequate oxygen use
- Systemic inflammatory response syndrome
- Diabetes mellitus
- Total parenternal nutrition
- Human immunodeficiency virus infection
- Drugs such as metformin, salicylate, antiretroviral agents, isoniazid, propofol, cyanide.

Figure 2: Figure taken from Strehlow, 2010. Multiple causes of elevated lactate levels (3).

Moreover, elevated lactate levels have been shown to predict mortality, independent of the cause of shock (4), hypotension and organ dysfunction (3).

In addition to lactate, other hematologic lab studies are used in shock to assess a patient's physiologic condition and detect abnormalities that require specific treatment (18). These abnormalities give clinicians clues to the organ system dysfunction that is either contributing to or resulting from the cause of shock (18). In the present study, we chose to analyze certain lab value

abnormalities in order to see what type of information they provide about physiologic instability in general. Specifically, we analyzed white blood cell count (WBC), troponin and lactate. Elevated WBC count is one of the SIRS criteria and is often used to diagnose sepsis, severe sepsis, and septic shock (14). A study by the Hisamuddin group showed that WBC count is an insensitive predictor of mortality in septic shock patients (14). However, our study investigates the prognostic value of WBC count in a much larger cohort of patients with physiologic instability. Moreover, we will be able to investigate the usefulness of WBC count in diagnosing septic shock as compared to other forms of shock. Troponin is the current golden standard for diagnosis of myocardial infarction (34). Because of this, we wanted to test its predictive value for cardiac etiologies of physiologic instability.

Additionally, we are working with the Wyss Institute who is developing new assay for the detection of live or dead bacterial components in the blood of infected patients. They are using this assay to ultimately create a dialysis system that filters bacteria from a patient's blood. The diagnostic portion of their assays may be a quicker way to diagnose septic shock by showing evidence of infection in a hematological test, delivering faster and more accurate results than a blood culture. Blood cultures are the current gold standard for diagnosing bacteremia, but they lack specificity and take time to process, which is not ideal for efficient treatment of hemodynamic dysfunction in the emergency department (15). The Wyss Institute's assay uses a magnetic bead based detection system to attach to

blood borne pathogens and a magnetic dialysis chamber to filter them out of the circulation. The magnetic beads are attached to Mannose Binding Lectin (MBL), which recognizes and attaches to large carbohydrates found on the surface of various pathogens. This test may have the potential to provide valuable and timely diagnostic information to the differentiation of physiologic instability. We chose to look at the sensitivity and predictive value of this novel test in the setting of physiologic instability.

The present study aims to analyze elements of the physical exam, medical history, vital signs, traditional labs and novel biomarkers to better understand and treat physiologic instability in the Emergency Department. Our study is unique for many reasons. The earliest form of diagnosis and treatment of critically ill patients is in the ED. However, research on Emergency Department patient populations is limited due to the fact that the clinical needs of the patients often takes priority over research in this setting (17). Moreover, there is a lack of research on patients with physiologic instability in general. Thus, this study aims to characterize the broad category of physiologic dysfunction; an imperative step in improving the treatment and outcomes for this poorly understood population.

OBJECTIVES

This study aims to characterize patients with physiologic instability by determining predictors of both its underlying etiology and clinical deterioration. We have expanded the category of shock to physiologic instability, so we can analyze a larger cohort of patients in order to discover early diagnostic and prognostic markers for shock, pre-shock, and other forms of physiologic dysfunction. The overall objective is to find factors that predict critical illness before it happens and to better diagnose it while its occurring.

In order to better understand and improve treatment for this population, we analyzed elements that are easily accessible to physicians in the emergency department early in the patients' visit, including elements from history, physical exam, vital signs, and traditional labs. We then determined the predictive value of these elements in determining the underlying etiology of undifferentiated physiologic instability (cardiogenic, septic, hypovolemic, anaphylactic, neurogenic, or other) as well as predict the likelihood of deterioration and mortality in these patients. In addition, as a preliminary proof-of-concept investigation, we analyzed the Wyss Institute's novel pathogen detection assay for its ability to predict septic etiology and clinical deterioration.

We hypothesized that there would be elements from the physical exam, history, and vital sign and traditional lab abnormalities that are both predictive of the underlying etiology of physiologic instability as well as the likelihood of clinical

deterioration in these patients. Furthermore, we hypothesized that the Wyss Institute's assay would demonstrate significant predictive value for septic etiology of physiologic instability, as well as the likelihood of clinical deterioration in this patient population.

METHODS

We performed a prospective observational study of patients who met predetermined physiologic instability in the emergency department at an urban, academic tertiary-care hospital with 55,000 annual visits. Physiologic instability was defined as any one of the following abnormalities: heart rate (HR) > 130, respiratory rate (RR>24), shock index (SI) > 1, systolic blood pressure (SBP) < 90 mm/hg, and Lactate > 4.0 mmol/L. The study design was approved by our institutional IRB with waiver of informed consent.

Patients were enrolled from November 15th, 2012 to March 1st, 2013. Patients were included in the study if they had any of the above mentioned vital sign abnormalities or elevated lactate for more than five minutes in the emergency department. Patients were excluded if the elevated HR was due to pain from simple trauma (i.e.: extremity fracture), atrial tachycardia with rapid ventricular response without other underlying cause, psychiatric agitation, intoxication or withdrawal, or isolated seizure.

Patients were identified and enrolled 24 hours a day in the study through the emergency department computer network, which through continuous surveillance identified any of the inclusion criteria abnormalities recorded in nursing notes, as well as any of these vital signs that were present on patient monitors for more than five continuous minutes. Identified patients were then included on a daily list. If patients were found to have any of the above described

exclusion criteria while their charts were being reviewed during data abstraction, they were not included in the study.

Data from enrolled patients were abstracted without knowledge of the subsequent hospital course or final diagnosis. Elements from the history of present illness, past medical history, medications, and physical exam were abstracted from the ED physician charts. If there was a discrepancy between attending and resident charts, the positive finding would be recorded as opposed to the negative finding. If the past medical history was not complete within the ED charts, than the discharge summary from a recent admission would be used to supplement the past medical history, but could not contribute to the history or present illness or physical exam. Demographic information, ED lab data, and data regarding the hospital stay (length of stay, ICU days, hospital disposition, and race) were matched to each patients from the hospital records.

The underlying cause of physiologic instability, categorized as: cardiogenic, septic, hemorrhagic, hypovolemic, anaphylactic, neurogenic, or other, was determined by an emergency physician through review of the hospital records after the patients visit to the Emergency Department. The physician recorded specific findings that lead them to their decision as well as record any evidence of deterioration, including acute renal failure (defined as at least two times the baseline creatinine levels) intubation, vasopressors, mortality and shock in the ED, that the patient showed during their time in the Emergency Department. Since there were so few patients were found with anaphylactic and

neurogenic shock, and their presentation is relatively obvious, we did not include them in the discriminatory analysis.

A convenience sample of patients who presented during the hours that research team members were in the hospital had wasted blood samples collected from the hospital laboratory. Samples were transferred to the Wyss Institute and analyzed within 24 hours. The Wyss Institute used a novel magnetic bead based detection system to determine the presence of live or dead bacteria in the whole blood of the patients. The magnetic beads were attached to Mannose-binding lectin protein, which recognizes and attaches to large carbohydrates found on the surface of various pathogens and a secondary antibody detection system was used to label the bound bacteria. The strength of signal given by the label was used to quantify the bound bacteria.

Study data were collected and managed using Redcap electronic data capture tools hosted at Beth Israel Deaconess Medical Center and analyzed using SAS 9.3 statistical software. Our primary outcome was the cause of instability, grouped as sepsis, cardiogenic, hemorrhagic, and hypovolemic. Our secondary outcome was clinical deterioration, which was a composite outcome of acute renal failure (creatinine two-times baseline), emergent intubation, use of vasopressors and death during the hospitalization. A variable number of patients did not have various lab studies sent. To account for these missing values, a new variable was created for missing troponin, lactate, and WBC. These missing values were analyzed similarly to the other covariates. A chi-squared analysis

was performed for each covariate for each cause of instability using $p<0.05$ to determine a significant association. Covariates that were significantly associated with a given cause of instability were then used to create a logistic regression model. Models were created using the cause of instability as the primary outcome, and a model was created for each cause. Beyond the significant covariates from the chi-squared, we also included age as a dichotomized covariate (>65 or ≤65 years old). We used the n/10 rule to determine the final number of covariates allowed into each model. Using the forward selection method, with $p<0.05$ for entry into the model. We then created a second model using our secondary outcome of clinical deterioration. Again, significant covariates from the chi-squared analysis were included in the building process, as well as dichotomized age, lactate >4, and hypotension. Again, forward selection with $p>0.05$ was used for entry into the model. The Wyss data was analyzed using a chi-squared test, with $p<0.05$ as the cutoff for significant.

RESULTS

Of the 540 eligible patients, 404 (74.8%) were included. The patients with physiologic instability included 181 (44.8%) patients with septic etiology, 54 (13.4%) patients with hypovolemic etiology, 49 (12.1%) patients with cardiogenic etiology, 26 (6.4%) patients with hemorrhagic etiology, and 94 (23.3%) patients with other etiology (Table 1 of Appendix). Patients were excluded for the following reasons: seizure (6), Intoxication (51), atrial fibrillation (35), supra-ventricular tachycardia (9), anxiety (23) and simple trauma (12) (Table 1 of Appendix). There were 169 (41.8%) males and 235 (58.2%) females in the study. The gender distributions for each category of physiologic instability are described in Table 2 of the Appendix. Our patient cohort was 4.2% Asian, 16.1% Black/African American, 6.9% Latino, 10.2% other, and 62.6% Caucasian. In Table 2 of the Appendix there is a description of patient race by etiology of physiologic instability. The average length of stay for the patients in our study was 5.7 ± 6.7 days and the average amount days these patients spent in the ICU were 1.7 ± 3.6 days. Refer to Table 2 of the Appendix for a description of length of stay and days spent in the ICU for each etiology of physiologic instability.

The first aim of this study was to predict the various underlying causes of physiologic instability. Physiologic instability caused by septic etiology (n=181) was significantly associated with a medical history of Human Immunodeficiency Virus (HIV), as well as antibiotic or oral steroid use upon admission into the ED

(Table 3). On the contrary, a past medical history of Congestive Heart Failure (CHF) showed a significant negative association with septic etiology of physiologic instability. History of present illness findings, including fever and cough were significantly associated with septic etiology, while blunt trauma showed significant negative association with septic etiology. Physical Exam findings, including fever > 100.4°F and cellulitis were also associated with septic etiology. Laboratory values, including: elevated WBC count and no troponin test performed on patient showed significantly correlated with septic etiology of physiologic instability (Table 4 of Appendix), while normal WBC count, no WBC count performed, and normal troponin levels showed significant negative correlation with septic etiology (Table 4 of Appendix).

Multivariable analysis determined the significant predictors for septic etiology of physiologic instability to include: history of present illness findings of fever and cough, physical exam findings of fever > 100.4°F and cellulitis, a lab finding of elevated WBC count, and a past medical history of HIV/AIDS (Table 5 of Appendix). Odds ratios and confidence intervals are reported for these covariates in Table 5 of Appendix.

As a preliminary proof-of-concept investigation, we enrolled 41 adults (age > 18 years) over a one-month period from the Beth Israel Deaconess Emergency Department. These patients showed unstable vital signs of any etiology of physiologic instability. The primary measurement was the Wyss bacterial detection assay. The etiology of illness was determined to be sepsis in 22/41

(54%), and 11/41 (27%) met the definition for clinical deterioration or death. The mean assay level was higher in patients with sepsis versus other etiologies of disease (mean 0.2 +/- .18 versus 0.12 +/-0.70, $p<0.05$). There was a trend towards higher levels in those with decompensation versus those without (0.27 +/- 0.23 versus 0.13 +/- 0.06, $p=0.06$). Finally, using the apriori defined threshold for a positive result of 2.0, of the 6 patients with a positive result, 5/6 (83%) had both sepsis as well as met the decompensation endpoints. However, the assay lacked overall sensitivity and specificity, which were 45.5% and 54.2%, respectively. Further development is warranted before it will achieve clinical utility.

A past medical history of myocardial infarction showed a significant association with physiologic instability caused by hypovolemia (n=49) (Table 6 of Appendix). Contrastingly, past medical history findings of COPD or liver disease were negatively associated with hypovolemic etiology (Table 6 of Appendix). History of present illness findings including nausea/vomiting and diarrhea were significantly associated with hypovolemic etiology, while fever, shortness of breath and cough showed significant negative associations with hypovolemic etiology (Table 7 of Appendix). A physical exam finding of abdominal tenderness was significantly associated with hypovolemic etiology, while fever > 100.4°F and crackles showed significant negative associations with hypovolemic etiology (Table 7 of Appendix).

The significant predictors for hypovolemic etiology of physiologic instability that were determined by multivariable analysis, included: a medical history finding of myocardial infarction and history of present illness findings of nausea/vomiting and diarrhea (Table 8 of Appendix). A history of present illness that included cough was a significant negative predictor hypovolemic etiology (Table 8 of Appendix). Odds ratios and confidence intervals are reported for these covariates in Table 8 of the Appendix.

A past medical history of liver disease was significantly associated with physiologic instability caused by hemorrhage (n=26) (Table 9 of Appendix). History of present illness findings, including: melena, vomiting blood and non-gastrointestinal bleeding were significantly associated with hemorrhagic etiology (Table 10 of Appendix). Contrastingly, fever showed a significant negative association with hemorrhagic etiology of physiologic instability. Rectal exam findings of bright red blood or melena showed significant associations with hemorrhagic etiology (Table 10 of Appendix).

The significant predictors for hemorrhagic etiology of physiologic instability determined by multivariable analysis, included: a history of present illness finding of a non-gastrointestinal bleed and rectal exam findings of bright red blood or melena (Table 11 of Appendix). Odds ratios and confidence intervals are reported for these covariates in Table 11 of Appendix.

A past medical history of Chronic Heart Failure (CHF) and Coronary Artery Disease (CAD) as well as anticoagulant use upon admittance to the ED were

significantly associated with physiologic instability of cardiogenic etiology (n=49) (Table 12), whereas a past medical history of liver disease showed a significant negative association with cardiogenic etiology (Table 13 of Appendix). History of present illness findings, including chest pain and shortness of breath were significantly associated cardiogenic etiology, while fever and melena showed significant negative associations with cardiogenic etiology (Table 13 of Appendix). Physical Exam findings including crackles and lower extremity edema were significantly associated with cardiogenic etiology, while fever and abdominal tenderness showed significant negative associations with cardiogenic etiology (Table 13 of Appendix). Laboratory values, including normal troponin and elevated troponin were significantly associated with cardiogenic etiology of physiologic instability, while having no troponin test performed showed a significant negative association with cardiogenic etiology (Table 13 of Appendix).

The predictors for cardiogenic etiology of physiologic instability that were found significant upon multivariable analysis, included: a medical history finding of Chronic Heart Failure (CHF), a history of present illness finding of shortness of breath and a physical exam finding of lower extremity edema (Table 14 of Appendix). Odds ratios and confidence intervals are reported for these covariates in Table 14 of the Appendix.

The second aim of this study was to predict clinical deterioration in patients with physiologic instability during their stay in the emergency department. Approximately 22.2% of the patients that qualified to be in our study

showed clinical deterioration. By etiology, they included: cardiogenic (26.5%), hypovolemic (20.4%), hemorrhagic (15.4%), septic (25.4%) and other (17%) (Table 15).

A past medical history of Coronary Artery Disease (CAD), hypertension, cancer, age > 65, and anticoagulant use upon admittance to the ED were significantly associated with physiologic instability that showed clinical deterioration (n=90) (Table 16 of Appendix). Physical Exam findings, including hypotension and altered mental status were significantly associated with clinical deterioration (Table 17 of Appendix). A laboratory finding of increased lactate showed a significant correlation with clinical deterioration in patients with physiologic instability. Contrastingly, no lactate measurement performed was significantly negatively associated with clinical deterioration (Table 17 of Appendix). The individual etiologies of physiologic instability showed no significant association with clinical deterioration (Table 17 of Appendix).

The predictors for clinical deterioration in patients with physiologic instability that were found significant upon multivariable analysis, included: hypotension, increased lactate and cancer (Table 18 of Appendix). Odds ratios and confidence intervals are reported for these covariates in Table 18 of Appendix.

LIMITATIONS

This study contained a number of limitations that should be considered when its results are interpreted. Misclassification may have occurred in the physician charts, which were abstracted for the covariates analyzed for association with physiologic instability etiology and outcomes. For convenience purposes, many of the chart fields in the software used to complete charts at BIDMC have automatically entered fields. Jugular venous distension and cold extremity temperature are not automatically filled out, and are therefore less likely to be on physician charts. This may have limited our analysis on these covariates, which have previously shown to significantly correlate with etiology of shock (19). Another important limitation of this study to note is errors during chart abstraction. The chart abstractions were completed by a non-physician who's limited medical knowledge may have caused error in interpretation of the charts. In order to avoid this type of error, a physician completed a random audit of the abstractions to be sure there were no mistakes identified. A third limitation that this study had was use of a single adjudicating physician to determine the cause of shock and the presence of deterioration. A system where multiple adjudicators were used and agreement tested would have improved this approach. The present study is a pilot study of a much larger cohort of patients. When the final study is completed, there will be two adjudicators for each patient.

DISCUSSION

The purpose of this study was to characterize physiologic instability in the emergency department by assessing factors that predict its causes and outcomes. Our data found that there are numerous positive and negative predictive factors for etiology of physiologic instability from elements of the past medical history, physical exam, and lab values which are all readily available to emergency department physicians. Furthermore, we also discovered elements from these exams that predict deterioration in this patient population. Our data support the significance of the medical history, physical exam, and traditional lab tests in treating patients with physiologic instability. These elements are some of the first available to ED physicians and with the time sensitive nature of treating patients with physiologic instability before any significant organ damage occurs (1, 3), they are ideal to integrate into a diagnostic and prognostic decision making to be used for treatment of physiologic instability in the ED.

The strengths of this study include its large cohort of patients, as well as the large number of covariates analyzed for their predictive value in diagnosing the underlying etiology of physiologic instability in addition to prognosticating patient outcomes. Many similar studies have investigated the usefulness of the patient history and physical exam in diagnosing shock or hemodynamic instability (5, 13, 19); however, they only looked at a small number of covariates in addition to more narrowly defined forms of instability (5, 13, 19).

Our criteria were broader and allowed us to analyze a wider range of disorders with various severities of illness. Since our patient cohort included shock and pre-shock, we were able to investigate warning signs that occur before critical illness ensues rather than having data that is limited to recognizing critical illness when it is already occurring. This is important due to the consensus among the literature that finds early treatment of shock leads to improved outcomes (1, 3). Moreover, the size of our patient cohort was much larger than in many of these studies, which added to the validity of our data.

An important issue with diagnosing the etiology of physiologic instability that our data addressed is the overlapping nature of the various etiologies (10, 11). In the univariate analysis of the associations between the abstracted covariates and each underlying cause of physiologic instability, there were many covariates that demonstrated significant positive associations with one etiology and significant negative associations with other etiologies. In this way, some significant covariates from this analysis could be distinguishing factors that rule out certain etiologies right away. For example, chronic heart failure is a significant negative predictor of septic etiology, but a significant positive predictor of cardiogenic etiology. Fever is a significant negative predictor of hypovolemic and hemorrhagic etiologies while it is a significant positive predictor of septic etiology. Nausea/vomiting is a significant negative predictor of septic etiology, and a significant positive predictor of hypovolemic etiology. Abdominal tenderness positively predicted hypovolemic etiology and negatively predicted

hemorrhagic etiology. Crackles positively predicted cardiogenic shock and negatively predicted hypovolemic shock. A past medical history of liver disease positively predicted hemorrhagic shock and negatively predicted both hypovolemic and cardiogenic shock. Cough positively predicted septic shock, and negatively predicted hypovolemic shock. These covariates could be used to in difficult cases of physiologic instability where the cause is not very obvious, to determine which cause is more likely.

By completing a multivariable logistic regression analysis on the covariates from the history, physical exam, and lab values, we determined which predictors for etiology of physiologic instability and clinical deterioration were the strongest prognostic and diagnostic predictors of physiologic instability. This will help to develop a strong diagnostic and prognostic tool for treating this population. The significant predictive factors for septic etiology which were determined by multivariable analysis, included: past medical history of HIV/AIDS, history of present illness findings of fever or cough, physical exam findings of fever > 100.4 and cellulitis, and an elevated WBC count. A WBC count that was not performed was a negative predictor of septic etiology. HIV/AIDS causes increased risk for infection, because it devastates the system by depleting CD4 positive T-cells (31). This explains the correlation between HIV/AIDS and septic etiology. Fever is a sign of the immune system fighting off infection, and cough often signifies a respiratory infection, unless it is chronic due to smoking, COPD or other disorders. Cellulitis is a skin infection and an elevated WBC count

signifies that the immune system is fighting off an infection. WBC counts are not performed in the ED if a patient has been transferred or if a physician does not request a WBC count for the patient. This negatively correlates with septic etiology, because if the physician does not think the patient need their WBC count tested, they probably already have a good idea that the patient is not infected.

Our experiments using the Wyss Institute's Mannose-binding lectin assay, show that it not yet sensitive or specific enough to replace bacterial cultures as the golden standard of infection diagnosis, and it was thus was a poor predictor of septic etiology of physiologic instability. However, because of the length of time it takes to grow a bacterial culture and the level of inaccuracy that occurs in blood cultures, it is not ideal for a golden standard (15). Moreover, it's not a very pragmatic test to use in the ED where the clinical needs of the patient are urgent and decisions need to be made quickly. The Wyss assay is a good step in the direction of developing better methods of diagnosing infection in patients, because it is quick and can completed simultaneously with multiple other hematological tests.

The significant predictive factors for hypovolemic etiology of physiologic instability determined by multivariable analysis, included: a past medical history of myocardial infarction, history of present illness nausea/vomiting or diarrhea. Cough showed significant negative predictive value for hypovolemic etiology. Myocardial infarction occurs when heart tissue is damaged due to ischemia. If

this damage is not severe enough to kill a patient, it can still heart dysfunction. This may not be directly linked to dehydration, but rather patients with a medical history of myocardial infarction may be more sensitive to dehydration. Nausea/vomiting and diarrhea are dangerously dehydrating mechanisms, and have a logical association with hypovolemic physiologic instability, which occurs when a patient has low blood volume (12). Cough is negatively associated with hypovolemic etiology of physiologic instability due to the fact that it is so strongly correlated with infection. Since hypovolemic etiology does not include infections, coughing has no compensatory function if hypovolemia is the underlying cause.

The significant predictive factors for hemorrhagic etiology of physiologic instability determined by multivariable analysis, included: rectal exam findings of melena or bright red blood, and non-GI bleeding. These findings all demonstrate very obvious bleeding mechanisms and since hemorrhagic physiologic instability occurs when there is a decrease in blood volume cause by bleeding (12), there is an obvious correlation between them.

The significant predictive factors for cardiogenic etiology of physiologic instability determined by multivariable analysis, included: a past medical history of chronic heart failure, a history of present illness finding of shortness of breath, a physical exam finding of lower extremity edema. Cardiogenic physiologic instability occurs when there is dysfunction with the heart, or the pump of the cardiovascular system (1). Congestive Heart Failure is a condition where the heart is unable to pump blood at a normal rate (33). This causes a backup of

blood in the circulatory system and the excess fluid can cause pulmonary edema as well as edema in other parts of the body (33). Congestive heart failure is associated with cardiogenic etiology because it is by definition a form of heart dysfunction. Shortness of breath occurs in cardiogenic etiologies of physiologic instability as a result of the body's compensatory mechanism to saturate the oxygen with blood and make up for the deficit occurring within the tissues due to the pump failure (7). Lower extremity edema occurs when the cardiovascular system is not functioning efficiently and blood flow is slowed. This causes blood to pool in the lower extremities, and the hydrostatic pressure of the blood in the vessels causes fluid movement into the tissues, or by definition, lower extremity edema (19).

The significant predictive factors determined by multivariable analysis for clinical deterioration in patients with physiologic instability included: hypotension (SBP < 90), increased lactate, and cancer. Hypotension is when there is a low systolic blood pressure caused by a decrease cardiac output (1). Hypotension is associated with poor outcomes (25) due to tissue hypoperfusion and sometimes organ failure and even death. If left untreated, hypotension can lead to irreversible problems and often by the time it is recognized, irreversible damage is already done (3). Consequentially, hypotension is associated with clinical deterioration. Increased lactate has been previously described as being associated with poor outcomes (4). Our study reinforced these findings. Cancer is one of the largest causes of mortality the United States, and though the cancer

death rate is decreasing, it is still substantial (32). Because there is no true cure for cancer, a large majority of cancer patients clinically deteriorate rather than improve. This explains the association of cancer with clinical deterioration.

The findings in this study are the beginning of the creation of an excellent diagnostic tool for determining the underlying cause of and the likelihood of clinical deterioration in patients with physiologic instability. This tool will improve treatment outcome in these patients, because efficient treatment leads to better outcomes (1, 3) and the ED is the first place where many of these patients are treated.

FUTURE DIRECTION

The current study is a pilot study for a much larger study. The final study will have a patient cohort of more than one thousand patients and two adjudicators per patient, improving the predictive value and accuracy of the current study. Furthermore, the larger study will investigate other potentially beneficial predictors of etiology and deterioration in patients with shock and pre-shock or physiologic instability.

For example, there is no single biomarker to distinguish between etiologies of shock (15). Even lactate is described as a nonspecific marker of shock and other critical illness (4). Therefore, in the larger study, we will analyze novel biomarkers in order to see if they have any value in predicting clinical deterioration or diagnosing the cause of physiologic instability. Procalcitonin (PCT) is not as commonly used in the United States as C-Reactive Protein (CRP), which is an acute phase reactant that responds to inflammation (22). One study found that CRP is a non-specific, insensitive marker to the various causes of fever, including systemic illness, auto-inflammatory syndromes, malignancy/chemotherapy, and tissue loss caused by ischemic or thromboembolic processes, and that PCT is a more accurate predictor (22). PCT is also superior to CRP in diagnosing sepsis, severe sepsis, and septic shock (23).

Furthermore, in an assay developed by the Hauser group, it is possible to distinguish SIRS caused by cell injury by detecting mitochondrial DAMPS, or endogenous damage-associated molecular patterns, from SIRS caused by infection, which can be detected though bacterial PAMPS, or microbial pathogen associated molecular patterns (24). This is very useful in distinguishing between etiologies of physiologic instability that show significant overlap, as well as deciding whether antibiotic treatment is necessary.

Some additional biomarkers that have been studied are endothelial cell markers. Endothelial dysfunction is a major contributor to the circulatory demise that occurs in septic shock. Inflammatory markers of endothelial dysfunction, including soluble intercellular adhesion molecule (ICAM-1), soluble vascular cell adhesion molecule (VCAM-1), the soluble vascular endothelial growth factor's (VEGF) soluble receptor (sFLT-1), E-selectin, and plasminogen activator inhibitor (PAI-1) have been previously investigated for their role in the various etiologies of shock (20). E-selectin facilitates cell endothelial adhesion to white blood cells, VCAM-1 and ICAM-1 which are located on the surface of endothelial cells and strongly bind to white blood cells so they can migrate into tissue from the blood stream, sFLT-1 is the soluble receptor for VEGF which also inhibits it, and PAI-1 regulates coagulation at the level of endothelial cells (20). Both E-selectin and sFLT-1 were found to be sepsis specific biomarkers when compared to other etiologies of hypotension (20).

Another biomarker, IL-6, also has been shown to have diagnostic and prognostic value in various shock states. (9, 21). Plasma levels of IL-6 predict mortality in some forms of cardiogenic shock (11), as well the likelihood of developing sepsis in infected patients (21). In addition, elevated IL-6 is also found in patients with other forms of physiologic instability not yet complicated by shock, like myocardial infarction (9). However, as previously discussed there is an overlap in the presence of inflammation in the different types of shock (11, 9). In addition, many of these biomarkers have not been studied in patients with pre-shock. Therefore, it is beneficial to revisit these biomarkers by exploring their role in a larger cohort of patients and in the broader category of physiologic instability.

Another part of the larger study will be to add minimally invasive methods for diagnosing and prognosticating physiologic instability, including Non-invasive Cardiac Output Monitoring (NICOM), extremity temperature, and echocardiography. Because these are quick and minimally invasive methods of monitoring hemodynamic functioning, they are ideal for use in the emergency department. NICOM is a non-invasive measure of cardiac output that has been validated clinically by being compared to cardiac output measured by thermodilution using a pulmonary artery catheter (28). In two studies by the Jones group, ultrasound was found to be useful in the diagnosis of undifferentiated hypotension (25, 26). Another study showed that NICOM is an important clinical tool, because cardiac output has more significant clinical

associations than systolic blood pressure, which is typically used to monitor hemodynamic functioning (29).

In addition, cold extremity temperature is shown to have prognostic value in patients with circulatory dysfunction (30). One study showed that since septic shock is associated with distributive malfunction, cold extremity temperature is not a predictor of poor microcirculation (27). This alludes to the possibility that extremity temperature may also have diagnostic value, as it will allow clinicians to distinguish between hemodynamic dysfunction that is septic or non-septic in etiology. These tools have not yet been integrated in a multivariable analysis with physical exam, patient history, and biomarker panels.

We plan to expand the current study, not only in patient volume, but also by creating a multifaceted diagnostic algorithm for the various forms physiologic instability that incorporates patient history, physical exam, biomarkers, and minimally invasive diagnostic methods. Adding biomarker panels and minimally invasive tools to the diagnostic and prognostic predictive elements from the patient physical exam and history will give us more insight into physiologic instability and how to best treat it.

APPENDIX: RESULTS TABLES

1. Inclusion and Exclusion

Included	404
Septic	181
Hypovolemic	54
Cardiogenic	49
Hemorrhagic	26
Other	94
Excluded	136
Seizure	6
Intoxication	51
Atrial Fibrillation	35
SVT	9
Anxiety	23
Simple Trauma	12
Total	540

Table 1: This table includes patients that met the inclusion criteria and the categories of physiologic instability they fall into, patients that were excluded from the study and reasons why there were excluded and total patients included in the present study.

2. Demographics of Patient Population

Variable	All Patients	Septic	Hypovolemic	Cardiogenic	Hemorrhagic	Other
N	404	181	54	49	26	94
Age	60 ± 20.1	59.5 ± 20.6	58.9 ± 20.4	69.1 ± 15.9	58.2 ± 23.1	54 ± 20.3
Gender						
Male	169 (41.8)	84 (46.4)	17 (31.5)	24 (49.0)	11 (42.3)	33 (35.1)
Female	235 (58.2)	97 (53.6)	37 (68.5)	25 (51.0)	15 (57.7)	61 (64.9)
Race						
Asian	17 (4.2)	6 (6.4)	2 (3.7)	0 (0)	3 (11.5)	6 (6.4)
Black/African American	65 (16.1)	21 (22.3)	10 (18.5)	9 (18.4)	4 (15.4)	21 (22.3)
Hispanic/Latino	28 (6.9)	18 (10.0	4 (7.4)	0 (0)	1 (3.9)	5 (5.3)
Other	41 (10.2)	23 (12.7)	4 (7.4)	5 (10.2)	1 (3.9)	8 (8.5)
Caucasian	253 (62.6)	113 (62.4)	34 (63.0)	35 (71.4)	17 (65.4)	54 (57.5)
Time in Hospital						
Length of Stay (Days)	5.7 ± 6.7	6.8 ± 7.5	4.1 ± 4.9	6.7 ± 5.0	5.3 ± 5.1	5.6 ± 10.8
Days Spent in ICU	1.7 ± 3.6	2.3 ± 5.3	0.7 ± 1.2	1.7 ± 2.9	1.7 ± 2.6	2.0 ± 5.8

Table 2: Demographics of Emergency Department patients included in the present Study

3. **Clinical Characteristics of Patients with Septic Etiology**

Coexisting Conditions	**Sepsis** *n = 181*	**Non-Sepsis** *n =223*	**P-value**
CHF	11%	23.2%	0.001* (-)
CAD	16%	16.6%	0.88
COPD	17.7%	11.2%	0.07
Dementia	8.3%	4.0%	0.07
Diabetes mellitus	23.2%	30.0%	0.12
Hypertension	46.4%	38%	0.09
Intravenous Drug Addiction	2.8%	2.7%	0.96
Liver Disease	6.1%	8.1%	0.44
PVD	6.6%	5.8%	0.74
Prosthetic Heart Valve	3.3%	0.5%	0.08
ESRD, no dialysis	2.2%	1.8%	0.77
ESRD, dialysis	8.3%	9.9%	0.58
Stroke	5.5%	3.1%	0.24
Myocardial Infarction	3.9%	8.1%	0.08
Immunosuppression			
None	55.3%	55.6%	0.94
Chemotherapy	6.1%	5.4%	0.76
Hematologic malignancy	3.9%	1.8%	0.20
HIV/AIDS	5.5%	1.4%	0.02*
Cancer	23.2%	28.3%	0.25
Metastatic Disease	4.4%	3%	0.50
Transplant	2.8%	2.2%	0.74
Splenectomy	0.6%	0%	0.27
Current Medications			
Anticoagulants	25.4%	25%	0.94
Antibiotics	18.2%	9.9%	0.02*
Oral Steroids	7.2%	15.7%	0.009* (-)

Table 3: Frequencies for covariates, including: coexisting conditions, immunosuppression, and current medications for patients with physiologic instability both with and without septic etiology. P-values < 0.05 show covariates are univariate predictors of septic etiology with 95% confidence.

4. Clinical Presentation of Patients with Septic Etiology

History	**Sepsis** *n = 188*	**Non-Sepsis** *n = 223*	**P-value**
Fever	55.3%	19.3%	<0.001*
Nausea/Vomiting	15.5%	23.8%	0.04* (-)
Diarrhea	7.7%	12.6%	0.11
Chest Pain	17.7%	25%	0.07
Shortness of Breath	33.2%	32.7%	0.93
Abdominal Pain	13.3%	18.4%	0.16
Cough	39.2%	23.3%	<0.001*
Dysuria	6%	7.2%	0.66
Melena	6%	7.2%	0.66
Vomiting Blood	0.9%	0%	0.20
Other Bleed	3.9%	5.4%	0.47
Rash	6%	5.8%	0.92
Blunt Trauma	0%	3%	0.016* (-)
Penetrating Trauma	0%	0%	1.0
Recent Surgery	2.2%	0.0%	0.26
Physical Exam			
Fever >100.4 °F	23.2%	2.7%	<0.001*
Altered Mental Status	13.3%	8.5%	0.12
Jugular Venous Distension	0.6%	1.4%	0.42
Crackles	12.2%	7.2%	0.09
Bilateral Lung Sounds	11%	5.8%	0.06
Heart Murmur	0%	0.5%	0.37
Rectal Exam-Bright Red Blood	1%	3%	0.17
Rectal Exam- Heme Positive	2.2%	3.6%	0.42
Rectal Exam- Melena	1.7%	1.8%	0.92
Abdominal Distension	2.8%	5.4%	0.19
Abdominal Tenderness	12.2%	14.4%	0.52
Lower Extremity Edema	11%	17.5%	0.07
Skin Mottling	1%	2.2%	0.38
Cellulitis	6.6%	1.4%	0.005*
Laboratory Values			
SIRS WBC	42.5%	23.8%	<0.001*
Normal WBC	51.4%	62.8%	0.02* (-)
Missing WBC	6.1%	13.5%	0.02* (-)
Elevated Troponin	3.9%	7.2%	0.15
Normal Troponin	10.5%	18.8%	0.02* (-)
Missing Troponin	85.6%	74%	0.004*

Table 4: Frequencies for covariates, including: history, physical exam and laboratory value findings for patients with physiologic instability both with and without septic etiology. Covariates with p-values < 0.05 show univariate predictive value for septic etiology with 95% confidence.

5. Clinical Characteristics that Predict Septic Etiology

Finding	Odds Ratio	Confidence Interval	P-value
History			
Fever	3.09	(1.8, 5.2)	<0.001*
Cough	1.7	(1.0, 2.9)	0.04*
Physical Exam			
Fever >100.5 °F	3.3	(1.9, 5.7)	<0.001*
Cellulitis	6.6	(1.7, 25.5)	0.006*
Laboratory Values			
SIRS WBC	2.1	(1.3, 3.5)	0.004*
Past Medical History			
HIV/AIDS	6.6	(1.6, 27)	0.009*

Table 5: Clinical findings showing multivariate predictive value for septic etiology. Odds ratios, 95% confidence intervals and p-values (significant p-value < 0.05) are reported.

6. Clinical Characteristics of Patients with Hypovolemic Etiology

Coexisting Conditions	**Hypovolemia** *n = 54*	**Non-Hypovolemia** *n =350*	**P-value**
CHF	24%	14.6%	0.20
CAD	22.2%	15.4%	0.21
COPD	1.9%	16%	0.005* (-)
Dementia	7.4%	5.7%	0.62
Diabetes mellitus	27.8%	26.9%	0.89
Hypertension	35.2%	42.9%	0.29
Intravenous Drug Addiction	3.7%	2.6%	0.63
Liver Disease	0%	8.3%	0.03* (-)
PVD	5.6%	6.3%	0.84
Prosthetic Heart Valve	0%	2.3%	0.26
ESRD, no dialysis	3.7%	1.7%	0.33
ESRD, dialysis	13%	8.6%	0.30
Stroke	3.7%	4.3%	0.84
Myocardial Infarction	13%	5%	0.03*
Immunosuppression			
None	53.7%	55.7%	0.78
Chemotherapy	9.3%	5%	0.22
Hematologic malignancy	3.7%	2.6%	0.63
HIV/AIDS	1.9%	3.4%	0.54
Cancer	29.6%	25.4%	0.51
Metastatic Disease	3.7%	3.7%	1.0
Transplant	1.9%	2.6%	0.75
Splenectomy	0%	0.3%	0.69
Current Medications			
Anticoagulants	22.2%	25.7%	0.58
Antibiotics	9.3%	14.3%	0.32
Oral Steroids	11%	12%	0.85

Table 6: Frequencies for covariates, including: coexisting conditions, immunosuppression, and current medications for patients with physiologic instability both with and without hypovolemic etiology. Covariates with p-values < 0.05 are univariate predictors of hypovolemic etiology with 95% confidence

7. Clinical presentation of patients with Hypovolemic etiology

History	Hypovolemia *n = 54*	Non-Hypovolemia *n = 350*	P-value
Fever	18.5%	38	0.005* (-)
Nausea/Vomiting	40.7%	16.9	<0.001*
Diarrhea	31.5%	7	<0.001*
Chest Pain	18.5%	22.3	0.53
Shortness of Breath	18.5%	35	0.02* (-)
Abdominal Pain	20.4%	15.4	0.36
Cough	11%	33.4	<0.001* (-)
Dysuria	1.9%	7.4	0.13
Melena	11%	6	0.16
Vomiting Blood	1.9%	0.3	0.13
Other Bleed	1.9%	5.1	0.29
Rash	5.6%	6	0.90
Blunt Trauma	1.9%	1.7	0.94
Penetrating Trauma	0%	0	1
Recent Surgery	0%	1	0.43
Physical Exam			
Fever >100.4 °F	0%	13.7%	0.004* (-)
Altered Mental Status	9.3%	10.9%	0.72
Jugular Venous Distension	0%	1.1%	0.43
Crackles	1.9%	10.6%	0.04* (-)
Bilateral Lung Sounds	1.9%	9.1%	0.07
Heart Murmur	0%	0.3%	0.69
Rectal Exam-Bright Red Blood	1.9%	2.3%	0.84
Rectal Exam- Heme Positive	5.6%	2.6%	0.23
Rectal Exam- Melena	0%	2%	0.30
Abdominal Distension	1.9%	4.6%	0.35
Abdominal Tenderness	22.2%	12.0%	0.04*
Lower Extremity Edema	6.8%	15.7%	0.11
Skin Mottling	1.9%	1.7%	0.94
Cellulitis	1.9%	4.0%	0.44
Laboratory Values			
SIRS WBC	24%	33.4%	0.17
Normal WBC	66.7%	56.3%	0.15
Missing WBC	9.3%	10.3%	0.82
Elevated Troponin	7.4%	5.4%	0.56
Normal Troponin	14.8%	15%	0.95
Missing Troponin	77.8%	79.4%	0.78

Table 7: Frequencies for covariates, including: history, physical exam and laboratory value findings for patients with physiologic instability both with and without hypovolemic etiology. Covariates with p-values < 0.05 show univariate predictive value for septic etiology with 95% confidence.

8. Clinical Characteristics that Predict Hypovolemic Etiology

Finding	Odds Ratio	Confidence Interval	P-value
History of Present Illness			
Nausea/Vomiting	2.5	(1.3, 4.9)	0.006*
Diarrhea	4.3	(2.0, 9.2)	<0.001*
Cough	0.34	(0.13, 0.90)	0.03* (-)
Past Medical History			
Myocardial Infarction	3.1	(1.1, 8.8)	0.03*

Table 8: Clinical findings showing multivariate predictive value for hypovolemic etiology. Odds ratios, confidence intervals and significant p-values ($p < 0.05$) are reported.

9. Clinical Characteristics of Patients with Hemorrhagic Etiology

Coexisting Conditions	Hemorrhage *n =26*	Non-Hemorrhage *n = 378*	P-value
CHF	19.2%	17.7%	0.85
CAD	7.7%	16.9%	0.22
COPD	15.4%	14%	0.85
Dementia	7.7%	5.8%	0.70
Diabetes mellitus	19.2%	27.5%	0.36
Hypertension	42.3%	34.6%	0.44
Intravenous Drug Addiction	0%	2.9%	0.38
Liver Disease	26.9%	5.8%	<0.001*
PVD	11.5%	5.8%	0.24
Prosthetic Heart Valve	0%	2%	0.45
ESRD, no dialysis	0%	2%	0.45
ESRD, dialysis	9.3%	7.7%	0.79
Stroke	0%	4.5%	0.27
Myocardial Infarction	6.4%	3.9%	0.61
Immunosuppression			
None	57.7%	55.3%	0.81
Chemotherapy	3.9%	5.8%	0.67
Hematologic malignancy	0%	2.9%	0.38
HIV/AIDS	0%	3.4%	0.34
Cancer	19.2%	26.5%	0.42
Metastatic Disease	0%	4%	0.30
Transplant	0%	2.7%	0.40
Splenectomy	0%	0.3%	0.79
Current Medications			
Anticoagulants	26.9%	25%	0.84
Antibiotics	19.2%	13.2%	0.39
Oral Steroids	19.2%	11.4%	0.23

Table 9: Frequencies for covariates, including: coexisting conditions, immunosuppression, and current medications for patients with physiologic instability both with and without hemorrhagic etiology. Covariates with p-values < 0.05 are univariate predictors of hemorrhagic etiology with 95% confidence

10. Clinical Presentation of Patients with Hemorrhagic Etiology

History	Hemorrhage *n = 26*	Non-Hemorrhage *n = 378*	P-value
Fever	15.4%	36.8%	0.03* (-)
Nausea/Vomiting	15.4%	20.4%	0.54
Diarrhea	11.5%	10.3%	0.84
Chest Pain	23%	21.7%	0.87
Shortness of Breath	19.2%	33.9%	0.12
Abdominal Pain	26.9%	15.3%	0.12
Cough	23%	30%	0.40
Dysuria	7.7%	6.6%	0.83
Melena	26.9%	5.3%	<0.001*
Vomiting Blood	3.9%	0.3%	0.01*
Other Bleed	23%	3.4%	<0.001*
Rash	11.5%	5.6%	0.21
Blunt Trauma	7.7%	1.3%	0.01*
Penetrating Trauma	0%	0%	1.00
Recent Surgery	0%	1%	0.60
Physical Exam			
Fever >100.4 °F	3.9%	12.4%	0.19
Altered Mental Status	0%	11.4%	0.07
Jugular Venous Distension	0%	1%	0.60
Crackles	3.9%	9.8%	0.32
Bilateral Lung Sounds	3.9%	8.5%	0.41
Heart Murmur	0%	0.3%	0.79
Rectal Exam-Bright Red Blood	15.4%	1.3%	<0.001*
Rectal Exam- Heme Positive	7.7%	2.7%	0.14
Rectal Exam- Melena	15.4%	0.8%	<0.001*
Abdominal Distension	11.5%	3.7%	0.05
Abdominal Tenderness	23%	12.7%	0.13
Lower Extremity Edema	7.7%	15%	0.30
Skin Mottling	3.9%	1.6%	0.39
Cellulitis	0%	4%	0.30
Laboratory Values			
SIRS WBC	26.9%	32.5%	0.55
Normal WBC	69.2%	56.9%	0.22
Missing WBC	3.9%	10.6%	0.27
Elevated Troponin	3.9%	5.8%	0.67
Normal Troponin	15.4%	15%	0.97
Missing Troponin	80.8%	79%	0.84

Table 10: Frequencies for covariates, including: history, physical exam and laboratory value findings for patients with physiologic instability both with and without hemorrhagic etiology. Covariates with p-values < 0.05 show univariate predictive value for hemorrhagic etiology with 95% confidence.

11. Clinical Characteristics that Predict Hemorrhagic Etiology

Finding	Odds Ratio	Confidence Interval	P-value
History			
Non-GI Bleeding	14	(4.5, 42.3)	<0.001*
Physical Exam			
Rectal Exam-Bright Red Blood	24	(5.7, 100.0)	<0.001*
Rectal Exam- Melena	40	(8.0, 197)	<0.001*

Table 11: Clinical findings showing multivariate predictive value for hemorrhagic etiology. Odds ratios, confidence intervals and significant p-values ($p < 0.05$) are reported.

12. Clinical Characteristics of Patients with Cardiogenic Etiology

Coexisting Conditions	**Cardiogenic** *n = 49*	**Non-Cardiogenic** *n = 355*	**P-value**
CHF	42.9%	14.4%	<0.001*
CAD	26.5%	14.9%	0.04*
COPD	18.4%	13.5%	0.36
Dementia	0%	6.8%	0.06
Diabetes mellitus	38.8%	25.4%	0.05
Hypertension	55%	40%	0.05
Intravenous Drug Addiction	0%	3%	0.21
Liver Disease	0%	8.2%	0.04* (-)
PVD	2%	6.8%	0.20
Prosthetic Heart Valve	2%	2%	0.97
ESRD, no dialysis	2%	2%	0.97
ESRD, dialysis	14.3%	8.5%	0.18
Stroke	4%	4.2%	0.96
Myocardial Infarction	12.2%	5.3%	0.06
Immunosuppression			
None	57%	55.2%	0.80
Chemotherapy	6%	5.6%	0.89
Hematologic malignancy	4%	2.5%	0.53
HIV/AIDS	0%	3.7%	0.17
Cancer	32.7%	25%	0.26
Metastatic Disease	4%	3.7%	0.88
Transplant	0%	2.8%	0.23
Splenectomy	0%	0.3%	0.71
Current Medications			
Anticoagulants	38.8%	23.4%	0.02*
Antibiotics	8.2%	14.4%	0.24
Oral Steroids	18.4%	11%	0.13

Table 12: Frequencies for covariates, including: coexisting conditions, immunosuppression, and current medications for patients with physiologic instability both with and without cardiogenic etiology. Covariates with p-values < 0.05 are univariate predictors of cardiogenic etiology with 95% confidence

13. Clinical Presentation of Patients with Cardiogenic Etiology

History	Cardiogenic *n = 49*	Non-Cardiogenic *n = 355*	P-value
Fever	18.4%	37.8%	0.008* (-)
Nausea/Vomiting	16.3%	20.6%	0.49
Diarrhea	4%	11.3%	0.12
Chest Pain	34.7%	20%	0.02*
Shortness of Breath	65.3%	28.5%	<0.001*
Abdominal Pain	8.2%	17.2%	0.11
Cough	30.6%	30.4%	0.98
Dysuria	8.2%	6.5%	0.66
Melena	0%	7.6%	0.05
Vomiting Blood	0%	0.6%	0.60
Other Bleed	6.1%	4.5%	0.62
Rash	6.1%	5.9%	0.95
Blunt Trauma	2%	1.7%	0.86
Penetrating Trauma	0%	0%	1
Recent Surgery	0%	1%	0.46
Physical Exam			
Fever >100.4 °F	4%	13%	0.07
Altered Mental Status	12.2%	10.4%	0.70
Jugular Venous Distension	2%	0.9%	0.43
Crackles	24.5%	7.3%	<0.001*
Bilateral Lung Sounds	6%	8.5%	0.58
Heart Murmur	0%	0.3%	0.71
Rectal Exam-Bright Red Blood	0%	2.5%	0.26
Rectal Exam- Heme Positive	0%	3.4%	0.19
Rectal Exam- Melena	0%	2%	0.32
Abdominal Distension	6%	3.9%	0.48
Abdominal Tenderness	4%	14.7%	0.04*
Lower Extremity Edema	40%	11%	<0.001*
Skin Mottling	2%	0%	0.32
Cellulitis	2%	3.9%	0.51
Laboratory Values			
SIRS WBC	22.5%	33.5%	0.12
Normal WBC	63.3%	56.9%	0.40
Missing WBC	14.3%	9.6%	0.31
Elevated Troponin	12.2%	4.8%	0.04*
Normal Troponin	44.9%	11%	<0.001*
Missing Troponin	42.9%	84.2%	<0.001*

Table 13: Frequencies for covariates, including: history, physical exam and laboratory value findings for patients with physiologic instability both with and without cardiogenic etiology. Covariates with p-values < 0.05 show univariate predictive value for cardiogenic etiology with 95% confidence.

14. Clinical Characteristics that Predict Cardiogenic Etiology

Finding	Odds Ratio	Confidence Interval	P-value
History			
CHF	3.01	(1.5, 6.2)	0.002*
Shortness of Breath	3.4	(1.7, 6.6)	<0.001*
Physical Exam			
LE Edema	3.6	(1.7, 7.4)	<0.001*

Table 14: Clinical findings showing multivariate predictive value for cardiogenic etiology. Odds ratios, confidence intervals and significant p-values ($p < 0.05$) are reported.

15. Etiology of Shock and Deterioration

Etiology	Patients showing Deterioration (n)	%
Cariogenic	13	26.5
Hypovolemic	11	20.4
Hemorrhagic	4	15.4
Septic	46	25.4
Other	16	17

Table 15: Frequencies of patients with various etiologies of physiologic instability that show clinical deterioration.

16. Clinical Characteristics of patients that Demonstrate Clinical Deterioration

Coexisting Conditions	**Deterioration** *n* = 90	**Non- Deterioration** *n = 314*	**P-value**
CHF	20%	17.2%	0.54
CAD	26.7%	13.4%	0.003*
COPD	18.9%	12.7%	0.14
Dementia	7.8%	5.4%	0.40
Diabetes mellitus	30%	26%	0.46
Hypertension	53.3%	38.5%	.01*
Intravenous Drug Addiction	3.3%	2.6%	0.69
Liver Disease	7.8%	7%	0.80
PVD	6.7%	6%	0.83
Prosthetic Heart Valve	1%	2.2%	0.50
ESRD, no dialysis	4.4%	1.3%	0.06
ESRD, dialysis	12.2%	8.3%	0.25
Stroke	7.8%	3.2%	0.06
Myocardial Infarction	5.6%	6.4%	0.78
Immunosuppression			
None	53.3%	56.1%	0.65
Chemotherapy	7.8%	5.1%	0.33
Hematologic malignancy	3.3%	2.6%	0.69
HIV/AIDS	2.2%	3.5%	0.54
Cancer	36.7%	23%	0.009*
Metastatic Disease	3.3%	3.8%	0.83
Transplant	1%	2.9%	0.34
Splenectomy	1%	0%	0.06
Current Medications			
Anticoagulants	36.6%	22.3%	0.01*
Antibiotics	14.4%	13.4%	0.79
Oral Steroids	7.8%	13%	0.17
Etiology			
Sepsis	51%	43%	0.17
Hemorrhage	4.4%	7%	0.38
Hypovolemia	12.2%	13.7%	0.72
Cardiogenic	14.4%	11.5%	0.45
Other	17.8%	24.8%	0.16

Table 16: Frequencies for covariates, including: coexisting conditions, immunosuppression, and current medications for patients with physiologic instability both with and without clinical deterioration. Covariates with p-values < 0.05 are univariate predictors of clinical deterioration with 95% confidence

17. Clinical presentation of patients that Demonstrate Clinical Deterioration

History	Deterioration *n = 90*	Non-Deterioration *n = 314*	P-value
Fever	31	36.6	0.33
Nausea/Vomiting	15.6	21.3	0.23
Diarrhea	13.3	9.6	0.30
Chest Pain	17.8	22.9	0.30
Shortness of Breath	35.6	32.2	0.54
Abdominal Pain	13.3	16.2	0.42
Cough	25.6	31.9	0.25
Dysuria	7.8	6.4	0.63
Melena	8.9	6	0.34
Vomiting Blood	0	0.6	0.45
Other Bleed	4.4	4.8	0.90
Rash	4.4	6.4	0.50
Blunt Trauma	1.1	1.9	0.61
Penetrating Trauma	100	100	1
Recent Surgery	0	1.3	0.28
Age > 65	61	40.1	<0.001*
Physical Exam			
Hypotension (SBP < 90 mmHg)	43.3	19.8	< 0.001*
Fever >100.4 °F	11	12.1	0.80
Altered Mental Status	17.8	8.6	0.01*
Jugular Venous Distension	2.2	0.6	0.18
Crackles	14.4	8	0.063
Bilateral Lung Sounds	11	7.3	0.25
Heart Murmur	0	0.3	0.59
Rectal Exam-Bright Red Blood	3.3	1.9	0.42
Rectal Exam- Heme Positive	3.3	96.7	0.82
Rectal Exam- Melena	2.2	1.2	0.69
Abdominal Distension	6.7	3.5	0.19
Abdominal Tenderness	12.2	13.7	0.72
LE Edema	20	13.1	0.10
Skin Mottling	1	1.9	0.61
Cellulitis	4.4	3.5	0.67
Laboratory Values			
Elevated Lactate	53.3	21.7	< 0.001*
Missing Lactate	16.7	37.9	<0.001*

Table 17: Frequencies, odd ratios and confidence intervals of history, physical exam, and laboratory value findings for patients with physiologic instability that demonstrate clinical deterioration. The odds ratios > 1 with a confidence intervals not including 1 show univariate predictive value for patients with physiologic instability that demonstrate clinical deterioration.

18. Clinical Predictors of Deterioration

Finding	Odds Ratio	Confidence Interval	P-value
Physical Exam			
Hypotension	2.8	(1.6, 4.7)	<0.001*
Laboratory Values			
Elevated Lactate	3.0	(1.7, 5.3)	<0.001*
Past Medical History			
Cancer	1.8	(1.1, 3.1)	0.03*

Table 18: Clinical findings showing multivariate predictive value for deterioration. Odds ratios, confidence intervals and significant p-values ($p < 0.05$) are reported.

19. Wyss Assay Results

Diagnosis	n	Wyss +
Sepsis	32	10
Cardiogenic	6	1
Hemorrhagic	3	1
Hypovolemic	14	4
Other	15	6

Table 19: Patient blood samples that were found positive using the Wyss Assay, organized by etiology of
physiologic instability.

20. The Wyss Assay and Predicting Sepsis

	Sepsis	Not sepsis
Wyss positive	10	22
Wyss negative	12	26
	Sensitivity	45.50%
	Specificity	54.20%

Table 20: The sensitivity and specificity of the Wyss Assay in predicting septic etiologies of physiologic instability.

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