Understanding Lactate in an Intensive Care Setting

by

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Abstract

We investigated the relationship between initial lactate levels and ICU patient outcomes using the MIMIC II (version 2.6) database. We divided ICU admissions based on their initial lactate measurement into three groups: admissions with high lactate (above 4.0 mmol/L), admissions with medium lactate (between 2.0 mmol/L and 4.0 mmol/L), and admissions with low lactate (below 2.0 mmol/L). In addition to the ICU population as a whole, we studied sepsis patients using three different criteria (Martin, Angus, and infection with SIRS).

We found that increased lactate levels were associated with a higher ICU mortality, higher 30 day mortality, longer ICU length of stay, and higher SOFA and SAPS I severity scores in all ICU admissions and in all three sepsis cohorts. Sepsis patients with high initial lactate levels were the most severely ill of all the patient populations. Sepsis patients identified with the Martin criteria who had high lactate levels had the worst outcomes of the three sepsis cohorts, but had similar average severity scores. This suggests that knowing lactate levels may give predictive value in addition to severity scores.

We also investigated the relationship between initial lactate, change in lactate from the first measurement to the second measurement, and ICU mortality. We found that patients with high initial lactate levels in combination with an increase in lactate level typically had poorer outcomes than patients with high initial lactate levels with a decrease in lactate level.

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Chapter 1

Introduction

1.1 Motivation

Lactate is a molecule continuously created in the body that has been used as a marker for declining health of intensive care unit (ICU) patients. Lactate has often been used as a surrogate for strained cellular metabolism and may have strong predictive value in determining outcome.

Clinicians consider persistent high lactate levels to be a sign of poor health. There have been many previous research studies focused on the predictive value of lactate clearance rates in ICU patients. Lactate levels can change very rapidly, so measurements need to be taken regularly in order to stay accurate. However, lactate cannot be measured without drawing arterial or venous blood which is a fairly invasive procedure that can lead to in hospital infections. Because of this risk, doctors may not order lactate levels to be measured as frequently, and they can miss rapid increases in lactate [1].

There have been few studies that focus on the predictive value of the initial lactate measurement in ICU patients. We believed that much could be learned about a patient's illness by knowing the initial lactate level, rather than waiting to see the change in lactate. In addition to lactate clearance rates, we were interested to see the association between the initial lactate level and patient outcome.

Gaining a better understanding of initial lactate measurements in ICU patients

may be useful to clinicians so that they may be able to predict outcome more effectively and be able to make better treatment plans. Quantifying the associations between initial lactate level and patient outcome may give insight as to how lactate levels can be used to diagnose illness in the ICU.

1.2 Thesis Outline

This thesis contains 7 chapters and one appendix. A brief overview of each chapter is as follows:

- Chapter 2: Background. This chapter reviews lactate metabolism and previous studies focused on lactate levels in ICU patients.

- Chapter 3: Methods. This chapter details the cohort we studied and the methods we followed to quantify relationships with lactate.

- Chapter 4: Lactate Associations in All ICU Patients. This chapter reviews all of the results we obtained when following our methods using a cohort of ICU patient.

- Chapter 5: Lactate Associations in Septic Patients. This chapter reviews all of the results we obtained when following our methods using cohorts sepsis patients in the ICU.

- Chapter 6: Discussion. This chapter analyzes and discusses the results found in Chapter 4 and 5.

- Chapter 7: Conclusions and Future Research Directions. This chapter summarizes this thesis and gives further research directions.

Chapter 2

Background

Accumulation of lactate in the body has been associated with poor outcomes in clinical settings. As the level of lactate increases above the normal range, the consequences increase in severity and outcomes are typically worse. Understanding lactate metabolism and its implications for the physiologic function of the body is very important for a patient's diagnosis and outcome.

2.1   Lactate Metabolism

Most cell energy is created in the form of ATP aerobically through the citric acid cycle and the electron transport chain. This process can only take place in environments with sufficient tissue resources and oxygen [2]. Pyruvate, created during glycolysis, is converted to acetyl CoA during the citric acid cycle, creating NADH. The overall reaction is as follows:

$$\text{pyruvate} + \text{NAD}^+ + \text{CoA} \longleftrightarrow \text{Acetyl CoA} + \text{CO}_2 + \text{NADH}$$
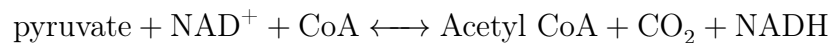
NADH is then sent to the electron transport chain where ATP is created through oxidative phosphorylation. In total through aerobic respiration, one glucose molecule creates 36 ATPs through glycolysis, the citric acid cycle and the electron transport chain.

If there is inadequate tissue perfusion or a lack of oxygen, the pyruvate created during glycolysis is instead converted anaerobically to lactate. Lactate dehydrogenase catalyzes the conversion between pyruvate and lactate as shown in Figure 1-1 [1]. NADH and a proton are consumed during this reaction. Only 2 ATP are created through substrate-level phosphorylation during glycolysis compared to the 36 ATP extracted during aerobic respiration.

Figure 2-1: Lactate production from pyruvate
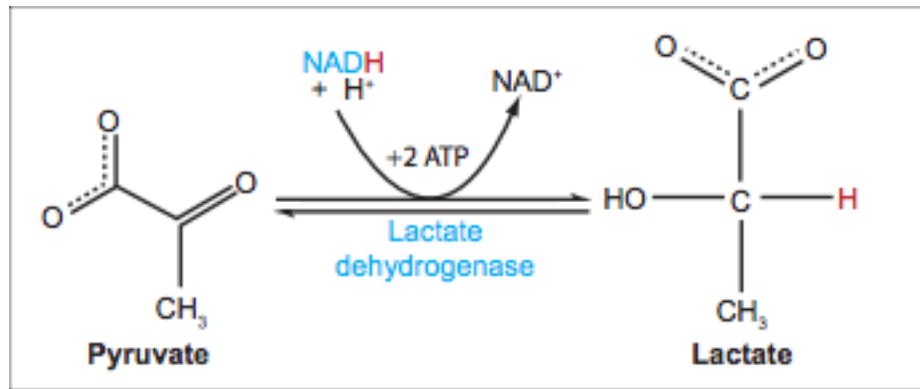
For every glucose molecule that goes through glycolysis and then undergoes anaerobic respiration, 2 lactate molecules are produced along with 2 protons and 2 ATPs. The overall reaction is as follows:

$$\text{glucose} + 2\,(\text{ADP} + \text{inorganic phosphate}) \longleftrightarrow 2\,\text{lactate} + 2\,\text{H}^+ + 2\,\text{ATP}$$

Even when oxygen is present, lactate is kept at a steady basal level in many tissues including skeletal muscle, the brain, kidneys, and red blood cells [2]. Daily, the human body creates approximately 20 mmol of lactate per kilogram of body weight. Lactate is also consumed at a high rate of about 320 mmol per liter per hour to keep levels low. Clearance of the created lactate keeps the level of lactate in the blood stable below 1 mmol per liter in normal conditions. Lactate is converted back to pyruvate through various processes such as gluconeogenesis in the liver and kidney and also the tricarboxylic acid cycle and oxidative phosphorylation in various organs throughout the body. Overall the liver is responsible for 70% of lactate clearance in the body. These processes keep the ratio of pyruvate to blood lactate at 10:1. Lactate is kept

constant in all tissues by lactate shuttles that help moderate the movement of lactate throughout the body. By these clearance processes, protons are also consumed which helps maintain acid-base homeostasis throughout the body.

2.2 Hyperlactatemia

Hyperlactatemia occurs when the production of lactate is greater than the consumption of lactate or clearance of lactate is malfunctioning. Hyperlactatemia implies addition of protons equal to the number of excess lactate molecules. The extra protons may cause an acid-base imbalance, so hyperlactatemia is also called lactic acidosis.

2.2.1 Causes

In normal situations, lactate can increase greatly but usually is consumed equally as quickly. During intense exercise, lactate concentration can increase by a factor of 100, but it quickly decreases back to normal levels after exercise. Shivering and seizures can also cause acute lactate increases, but they are normally cleared quickly.

Various other disorders account for more serious lactic acidosis. Lactic acidosis can be divided into two types. Lactic acidosis is type A if its cause is associated with tissue hypoxia, and it is type B if there is no tissue hypoxia [2]. A patient may have both types if multiple causes are contributing to the overproduction of lactate. The most common causes of hyperlactatemia are cardiogenic shock, severe heart failure, trauma, and sepsis.

Causes of increased lactate production can further be divided into three main categories: Demand, Delivery, and Utilization [1]. Increased demand for oxygen, inadequate oxygen delivery to tissues, and inadequate utilization of oxygen all contribute to the production of lactate. Table 1.1 shows specific disorders corresponding to each cause of lactic acidosis. Drugs affecting utilization that may cause lactic acidosis include Metformin, nucleoside reverse-transcriptase inhibitors, and propofols. These drugs interfere with oxidative phosphorylation causing lactate to be produced anaerobically. Thiamine deficiency causes reduction of pyruvate dehydrogenase activity,

Inadequate Delivery of O_2	Increased Demand for O_2	Inadequate Utilization of O_2
Volume depletion	Shivering	SIRS
Significant blood loss	Seizures	Diabetes mellitus
Septic shock	Strenuous exercise	Thiamine Deficiency
Profound anemia		HIV infection
Severe hypoxemia		Certain drugs
Carbon monoxide exposure		
Trauma		

Table 2.1: Causes of Hyperlactatemia

thus increasing lactate production.

There are a few causes that also do not fit into any of the three categories mentioned. Cancer can cause an increase in glycolysis in a tumor, and the excess product is converted to lactate. In liver disease and severe liver cancer, the clearance of lactate decreases which overall increases the amount in the body. Multiple disorders may act at the same time to increase lactate levels even more significantly.

2.2.2 Treatment

Hyperlactatemia has been associated with poor outcomes in clinical settings, so monitoring high lactate levels is a main priority. Normal blood lactate levels range from approximately 0.5 mmol per liter to an upper limit of 2.0 mmol per liter. Lactate in a patient can be measured either in venous or arterial blood. Knowing the underlying cause of the increased lactate concentration is very important in determining treatment [2].

When oxygen delivery is the main cause of lactic acidosis, restoring tissue perfusion is very important. Oxygen delivery can depend on cardiac output, hemoglobin, or the partial pressure of oxygen in the blood. Vasopressors and other agents are often used to help restore perfusion in cases of low blood pressure. In situations where sepsis is the main cause, antibiotics are given to help treat the underlying infection causing

the lactate increase. Treating the main cause is often how increased lactate levels are addressed in a clinical setting.

2.3   Role of Lactate in Emergency Medicine

In the emergency department, knowing a patient's lactate levels may provide useful information for treatment and predicting outcome. Studies have shown that an increased lactate level is associated with increased mortality in patients that have sepsis, and the higher the lactate level, the worse the outcome will be. In addition, studies have been done to show that if lactate is cleared within a short period of time (about 24 hours), the outcome is much more likely to be positive. Lactate measurements provide physicians with information about the patient's cellular metabolism and the overall severity of their illness especially in sepsis or trauma patients.

In situations of severe injury, lactate levels give information about how cellular metabolism is affected and can be used to predict outcome. In 1993, Abramson et al. performed a study looking at the survival rates of 76 trauma patients admitted into the Intensive Care Unit (ICU) [3]. All of the 27 patients whose lactate cleared to a normal level below 2.0 mmol per liter within 24 hours survived. When lactate was cleared between 24 and 48 hours, only 75% survived, and when lactate was not cleared within 48 hours only 14% survived (3 out of 22). They concluded that lactate clearance time was very important in determining patient outcomes, while initial lactate measurement did not seem as helpful.

Shapiro et al. found a connection between lactate level and mortality when studying 1,278 patients with infections [4]. Patients with a lactate level less than 2.5 mmol per liter had a mortality rate of only 4.9% whereas patients with lactate over 4 mmol per liter had a mortality rate of 28.4%. As lactate levels increased, the outcomes became worse.

2.3.1 Sepsis

In the United States, severe sepsis has become a very prevalent syndrome that has become a large focus in medicine. In 2001, Angus et al. concluded that there were over 750,000 cases of severe sepsis in the United States each year, and since then the prevalence has only increased [5]. Severe sepsis patients account for 2% of all patients that are admitted to the hospital and of those patients half of them are admitted into the ICU. Severe sepsis patients represent 10% of all ICU admissions. Understanding sepsis and its causes is important for improving outcomes and diagnosis.

Sepsis, Severe Sepsis, and Septic Shock

Sepsis is defined as a systemic inflammatory response to infection. For a patient to be considered septic, they must have a documented or suspected infection and have signs of systematic inflammatory response syndrome (SIRS) [6]. SIRS is diagnosed when a patient has two or more of the following symptoms: body temperature less than 36°C or greater than 38°C, heart rate above 90 beats per minute, respiratory rate higher than 20 per minute or partial pressure of carbon dioxide lower than 32 mmHg, white blood cell count higher than 12,000 cells per microliter or lower than 4,000 cells per microliter or greater than 10% immature (band) forms. The most common cause of infection in septic patients is pneumonia which is associated with half of all cases. Intrabdominal and urinary tract infections are the next most common causes. Infections causing sepsis can be acquired in the community and also in health care facilities.

Sepsis can become very critical if it is not treated quickly; patients may become severely septic or go into septic shock. Severe sepsis is defined as sepsis complicated by organ dysfunction, and septic shock is defined as sepsis with persistent arterial hypotension. Hypotension is defined as systolic arterial pressure below 90 mmHg, mean arterial pressure lower than 60 mmHg, or a reduction in systolic blood pressure of more than 40 mmHg. Persistent hypotension refers to hypotension that persists even after volume resuscitation [7]. Table 1.2 summarizes the criteria of sepsis, severe

sepsis, and septic shock.

Table 2.2: Criteria for SIRS, Sepsis, Severe Sepsis, and Septic Shock

Term	Criteria
SIRS	At least 2 of the following: • Temperature $> 38°$C or $< 36°$C • Heart rate > 90/min • Hyperventilation evidenced by respiratory rate >20/min or arterial CO_2 lower than 32 mmHg • White blood cell count >12000 cells/μL or lower than 4000 cells/μL or $>10\%$ immature band forms
Sepsis	SIRS criteria with suspected or proven infection
Severe Sepsis	Sepsis with organ dysfunction
Septic Shock	Sepsis with hypotension despite adequate fluid resuscitation

Lactate in Sepsis Patients

Studies have been done to show the importance of lactate in diagnosing and treating severe sepsis and septic shock. In an analysis of 20 hemodynamic variables and organ dysfunction variables, lactate was found to be the only easily determined parameter that was helpful in the prediction of outcome in septic patients [8]. Lactate has been found to be an important parameter for indicating sepsis induced hypoperfusion and also an important indicator for early goal directed therapy of sepsis. An increase in lactate in septic patients may not be due to decreased perfusion though, and it may be due to cellular dysfunction resulting from toxins instead.

The rate of clearance of lactate has been associated with the outcomes of patients. Nguyen et al. studied the lactate clearance of 111 ICU patients that had either severe sepsis or septic shock. Lactate clearance was defined as the percent decrease in lactate

after 6 hours. They found that as lactate clearance increased, mortality decreased. For approximately every 10% increase in lactate clearance, there was an 11% decrease in mortality rate. In contrast to Shapiro et al., Bakker et al. found that initial blood lactate levels were not predictive of outcome, but the time to decrease lactate levels was more indicative of outcome. The role of lactate in predicting mortality is still not fully understood.

2.4   Thesis Goals

First, we were interested in quantifying the relationship between lactate and other easily measured parameters in ICU patients to access the predictive value of initial lactate levels in the ICU. More concretely, we wanted to more fully understand the association between initial lactate levels and ICU mortality, 30 day mortality, length of stay, and severity of illness. We wanted to quantify differences in patient outcome associated with differing levels of initial lactate. We focused on three different ranges of lactate levels: low (below 2.0 mmol/L), medium (between 2.0 mmol/L and 4.0 mmol/L), and high (above 4.0 mmol/L).

Our next goal was to identify sub-populations whose lactate levels were more associated with mortality and severity of illness. In order to achieve this goal, we found which conditions were most commonly associated with high lactate levels. We hypothesized that patients in certain care units might be more likely to have high lactate levels than others. To test this hypothesis, we specifically analyzed lactate associations with ICU mortality, 30 day mortality, length of stay, and severity of illness in each care unit of the ICU separately. Lastly, we analyzed the role of lactate in sepsis patients. Because there are multiple ways to define sepsis patients, we identified three different cohorts of patients with sepsis and analyzed their lactate levels.

Finally we wanted to determine if knowing change in lactate gave additional predictive value to the initial lactate value. We focused on the implications of lactate change in combination with the level of the initial lactate on ICU mortality. Previous studies showed that change in lactate is important for predicting patient outcome, so

we were interested to see the effect of controlling for the initial lactate measurement.

Chapter 3

Methods

We studied the association of lactate levels with ICU mortality, 30 day mortality, length of stay, and illness severity. In addition, we studied how lactate clearance rates were associated with ICU mortality. We analyzed the associations of lactate in all ICU patients and also in the sub-cohort of septic patients because of the previous studies investigating the association of lactate levels to patient outcome. The goal of this study was to better understand the predictive value of lactate in an intensive care setting.

3.1   Cohort

Patient information used in this investigation was provided by the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) II database (version 2.6) [9]. The online database contains records of 32,536 patients admitted to the ICU of Beth Israel Deaconess Medical Center in Boston, Massachusetts. There is detailed information about each of the 40,426 ICU stays including care unit, lab work, vitals, nursing notes, etc. which can be extracted for research and analysis.

3.2 Initial Lactate Measurements

Initially we identified which patients (based on their ICU stay ID) had lactate measurements made during their ICU admission. Using the Lab Events table in the MIMIC II database, we found the first lactate measurement for each ICU admission. We also identified patients who did not have lactate measurements during their ICU stays. We looked specifically at the initial lactate measurement to understand further if it had any predictive value. We found 14,402 ICU admissions in which the patient had lactate measured, and 26,024 admissions where no measurement was taken.

Based on previous studies, we divided the group of ICU admissions into three groups based on their initial lactate measurements: lactate less than 2.0 mmol/L, between 2.0 mmol/L and 4.0 mmol/L, and greater than 4.0 mmol/L. Lactate levels under 2.0 mmol/L are considered normal whereas lactate levels of 4.0 mmol/L or greater are considered very high. There were 8,107 admissions with initial lactate levels less than 2.0 mmol/L, 4,055 admissions with lactate levels between 2.0 mmol/L and 4.0 mmol/L, and 2,240 admissions with lactate levels above 4.0 mmol/L. The cohort breakdown is shown in Table 2.1.

Table 3.1: Cohort broken down into groups by lactate measurement

Initial Lactate Value	Number of ICU Admissions	Percent of Cohort
$\leq$2.0 mmol/L	8,107	20.1%
$>$ 2mmol/L and $<$ 4.0 mmol/L	4,055	10.1%
$\geq$ 4.0 mmol/L	2,240	5.5%
No Lactate Measurement Taken	26,024	64.3 %

3.3 Parameters Compared to Lactate

3.3.1 ICU Mortality

To determine ICU mortality, we used the ICU expire flag in the ICU Stay Events Detail table. We compared the lactate measurement and ICU expire flag based on a shared ICU stay ID. The ICU mortality rate was the number of ICU admissions where the patient died in the ICU compared to the overall number of ICU admissions.

3.3.2 30 Day Mortality

For 30-day mortality, first we checked if the patient had a date of death on record. If the patient's date of death was within 30 days of their discharge from the ICU, they were counted as dead within 30 days.

3.3.3 Length of Stay

When determining length of stay, we found the average and the median length of stay of all of the ICU admissions corresponding to the ICU stay IDs in each group of patients we considered. We only included patients who did not die during their ICU stay. We looked only at survivors in order to use length of stay as a surrogate for how sick a patient was.

3.3.4 Severity of Illness

In order to understand the association between lactate levels and severity of illness, we looked at the first SAPS I and first SOFA severity scores of each ICU admission and compared them to the initial lactate level. The SAPS I score is used to classify how likely a patient is to die while in the ICU [10]. The SAPS I score is based on 14 measured clinical variables and is not based on diagnosis. The SOFA score is another prognostic indicator used in the ICU [11]. The SOFA score was originally created in order to assess the organ failure status of a patient.

3.4   Conditions Associated with High Lactate

Patients who enter the hospital are billed according to the illnesses they are treated for and the procedures they have done while at the hospital. The system in place in the United States to assign codes to diseases and procedures is the International Classification of Diseases, Ninth Revision (ICD-9) [12]. These codes are used to determine how a patient will be billed. In retrospective research studies, these billing codes are often used to see why a patient was in the hospital and what the major conditions were for which they were treated while at the hospital. We identified the ten most common primary ICD-9 codes associated with ICU admissions that had an initial lactate greater than 4.0 mmol/L. We wanted to gain a better understanding of the main causes for high lactate levels.

3.5   Change in Lactate

In addition to looking at initial lactate measurements,we also compared change in lactate level to ICU mortality in order to gain a better understanding of why some people with high initial lactate died while others did not. In previous studies, evidence showed that high initial lactate levels were associated with higher rates of ICU mortality so we decided to look at the relationship between high initial lactate and change in lactate. We determined the percent change in lactate from the initial lactate measurement to the second measurement for patients who had their lactate measured two or more times throughout their ICU stay. We found the first two lactate measurements for each ICU stay and calculated clearance as:

$$(Lactate_{second} - Lactate_{first})/(Lactate_{first}) * 100$$

We compared ICU mortality rate to the change in lactate to try to better understand why some people with high initial lactate levels die while others live.

3.6 Septic Cohort

To further investigate lactate's predictive value, we looked specifically at septic patients because of previous associations made between sepsis and lactate. In order to characterize the septic population, we identified three different septic cohorts by using different criteria. We used both Angus and Martin criteria for identifying patients with severe sepsis. In addition we identified a septic cohort based on the presence of infection and systemic inflammatory response syndrome.

3.6.1 Martin Implementation

The Martin definition of severe sepsis is based on ICD-9 codes for sepsis as well as ICD-9 codes and procedure codes for organ dysfunction [13]. To be considered severely septic, the patient needs an ICD-9 code for septicemia (038), septicemic (020.0), bacteremia (790.7), disseminated fungal infection (117.9), disseminated candida infection (112.5), or disseminated fungal endocarditis (112.81). In addition to one of the previous codes, the patient needs a code representing organ dysfunction.

Because a patient may only be billed for a set number of conditions during each hospital visit, some septic patients may not have a billing code specifically for sepsis. If the patient has other serious conditions, the assigned codes may not include sepsis even when the patient had the diagnosis during their hospital stay.

3.6.2 Angus Implementation

The Angus implementation for identifying severely septic patients also uses ICD-9 codes to determine how a patient was diagnosed while at the hospital. Instead of using codes specifically for sepsis, the implementation finds patients who have a code for a bacterial or fungal infection and acute organ dysfunction – two of the main criteria for diagnosing severe sepsis [5]. To be identified as severely septic in our cohort, a patient needed to have at least one ICD-9 code from each category of codes (infection and organ dysfunction). The Angus implementation of the definition of severe sepsis has been found to be reasonably accurate at identifying patients with

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severe sepsis, but it is imperfect[14].

3.6.3   Infection and SIRS

We defined a cohort based on the definition of sepsis, rather than based on ICD-9 codes. We found patients that had a confirmed or suspected infection as well as two out of the four SIRS criteria, defined in Chapter One. We decided to look at just patients who were septic at the onset of their ICU admission as an ad hoc decision because it was simplest.

To determine either confirmed or suspected infection, we looked at whether the patient was started on IV antibiotics within the first 24 hours of admission to the ICU. The list of antibiotics we considered are located in section A.1.

We also determined whether the patient had two of the four SIRS criteria at relatively the same time during the first day of the ICU stay. We found each time the patient had their heart rate, temperature, white blood cell count, or respiratory rate measured. If two of the patient's measurements met the criteria and were measured within eight hours of each other, the patient was considered to have SIRS.

If the patient had SIRS and had a confirmed or suspected infection on the first day, we considered the patient to have sepsis on the first day of admission. When comparing lactate measurements within this cohort, we only looked at initial lactate measurements taken on the first day of the ICU stay, to remain consistent with how the cohort was chosen. Therefore, the lactate measurements were taken at the same time as the suspected sepsis.

We evaluated our selected cohort by examining ten randomly selected cases from the cohort. We looked at the nursing notes and discharge summaries associated with each of the ten admissions, and we found in each case evidence of sepsis or of the implementation of the septic protocol.

The criteria used to find this cohort is the least stringent of the three methods because it may capture patients who had suspected sepsis but in the end did not actually have sepsis.

Chapter 4

Lactate Associations in All ICU Patients

4.1 Associations with Initial Lactate Levels

There were 40,426 ICU admissions in total in our cohort. Of these admissions, there were 14,402 ICU admissions that had lactate measurements (35.6%) and 26,024 ICU admissions that did not have lactate measurements (64.4%).

4.1.1 ICU Mortality Rate

Compared to the overall ICU mortality of all ICU admissions, 5.8%, the ICU mortality rate of ICU admissions that had lactate measured was much higher at 13.1%. Those who did not receive a lactate measurement had a very low ICU mortality rate of 1.8%. This may suggest that only patients who were very ill had their lactate measured. All ICU mortality rate results are detailed in Table 4.1.

We found that as initial lactate levels increased, so did the ICU mortality rate. Notice in Table 4.1 that admissions with normal lactates (lactate level less than or equal to 2.0 mmol/L), the ICU mortality rate was only 9.6% whereas admissions with high lactate (lactate level greater than 4.0 mmol/L) had a much larger ICU mortality rate of 26.8%. The ICU mortality rate of those with initial lactate levels between

2.0 mmol/L and 4.0 mmol/L was 12.5%, which was higher than that of those with normal lactate levels, but much lower than that of patients with very high lactate levels.

Table 4.1: ICU Mortality Vs. Lactate for All ICU Admissions

	Died in the ICU	Did not Die in the ICU	Total ICU admissions	ICU Mortality Rate
Initial Lactate ≤ 2.0 mmol/L	776	7,331	8,107	9.60%
Initial Lactate > 2.0 mmol/L and < 4.0 mmol/L	506	3,549	4,055	12.50%
Initial Lactate ≥ 4.0 mmol/L	600	1,640	2,240	26.80%
Any Lactate Measurement	1,882	12,520	14,402	13.10%
No Lactate Measurement	469	25,555	26,024	1.80%
All ICU Admissions	2,351	38,075	40,426	5.80%

4.1.2 30 Day Mortality Rate

In general, the 30 day mortality rates were approximately twice the ICU mortality rates, but they still followed the same trend. The 30 day mortality rate of those with any lactate measurement was much higher than the rate of all ICU admissions whereas the 30 day mortality rate of those without a lactate measurement was much lower. Admissions with a lactate measurement had a 30 day mortality rate of 22.5%, compared to those without a lactate measurement which had a 30 day mortality rate of only 5.9%. Again, the results suggest that patients who were not as sick did not

get their lactate measured. All 30 day mortality results are detailed in Table 4.2.

As initial lactate level increased, so did the 30 day mortality rate. Admissions with initial lactate less than 2.0 mmol/L had a 30 day mortality rate of 17.5%. Admissions with initial lactate above 4.0 mmol/L had the highest 30 day mortality rate of 41.6%.

Table 4.2: 30 Day Mortality Vs. Lactate for All ICU Admissions

	Died within 30 Days	Did not Die within 30 Days	Total ICU admissions	30 Day Mortality Rate
Initial Lactate ≤ 2.0 mmol/L	1,416	6,691	8,107	17.5%
Initial Lactate > 2.0 mmol/L and < 4.0 mmol/L	885	3,170	4,055	21.8%
Initial Lactate ≥ 4.0 mmol/L	932	1,308	2,240	41.6%
Any Lactate Measurement	3,233	11,169	14,402	22.5%
No Lactate Measurement	1,817	24,207	26,024	7.0%
All ICU Admissions	5,048	35,378	40,426	12.5%

4.1.3   Length of Stay

Compared to length of stay of all ICU admissions who survived which had an average of 5.4 days and a median of 2.0 days, admissions with any lactate measurement had a longer length of stay than those without a lactate measurement. This may suggest that admissions with lactate measurements were sicker on average than those who did not. All length of stay results of ICU survivors are summarized in Table 4.3.

ICU admissions in which the patient survived their ICU stay, who had an initial

lactate level below 4.0 mmol/L, all had similar lengths of stay. The average and median length of stay for those with initial lactate below 2.0 mmol/L was 6.6 and 3.4 days respectively, and the average and median length of stay for those with initial lactate between 2.0 mmol/L and 4.0 mmol/L was 6.6 and 3.2 days. Admissions with initial lactate above 4.0 mmol/L had a slightly longer length of stay with an average of 7.4 days and a median of 3.9 days.

Table 4.3: Average and Median Length of Stay Vs. Lactate for All ICU Admissions Who Survived Their ICU Stay

	Average Length of Stay (Days)	Median Length of Stay (Days)
Initial Lactate ≤ 2.0 mmol/L	6.6	3.4
Initial Lactate >2.0 mmol/L and <4.0 mmol/L	6.6	3.2
Initial Lactate ≥ 4.0 mmol/L	7.4	3.9
Any Lactate Measurement	6.9	3.4
No Lactate Measurement	4.7	1.5
All ICU Admissions	5.4	2.0

4.1.4 Severity of Illness

As a surrogate for severity of illness, we determined the average SOFA score and SAPS I scores of ICU admissions with lactate levels. Admissions with any lactate measurement had much higher severity scores than admissions without a lactate measurement, as seen in Table 4.4. We saw greater likelihood of mortality, based on these scores, in patients with higher lactate levels. Admissions with initial lactate levels less

than 2.0 mmol/L had an average SOFA score of 6.50 and an average SAPS I score of 14.88. Admissions with high initial lactate levels above 4.0 mmol/L had the highest average severity scores, a 10.05 SOFA score and a 19.23 SAPS I score. The average SOFA score and SAPS I score for all ICU admissions with a lactate measurement were 7.41 and 15.91, respectively. Table 4.4 summarizes the average severity scores.

Table 4.4: Average SOFA and SAPS I Scores Vs. Lactate for All ICU Admissions

	Average SOFA Score	Average SAPS I Score
Initial Lactate ≤ 2.0 mmol/L	6.50	14.88
Initial Lactate >2.0 mmol/L and <4.0 mmol/L	7.75	16.18
Initial Lactate ≥ 4.0 mmol/L	10.05	19.23
Any Lactate Measurement	7.41	15.91
No Lactate Measurement	3.91	11.6
All ICU Admissions	5.54	13.7

4.1.5   Change in Lactate

When initial lactate was below 2.0 mmol/L, we saw a slight increase in ICU mortality when the second lactate level increased, but the ICU mortality rate stayed under 20% for all changes in lactate level as shown in Figure 4-1. When initial lactate levels were between 2.0 mmol/L and 4.0 mmol/L, there was a greater increase in ICU mortality rate when lactate increased rather than decreased as shown in Figure 4-2. An increase in lactate of more than 80% had an ICU mortality rate of 34.62%.

The greatest difference in ICU mortality rates was seen in admissions with initial

lactate greater than 4.0 mmol/L. The ICU mortality rate continuously increased as the percent change in lactate increased as seen in Figure 4-3. When lactate levels decreased by more than 80%, the ICU mortality rate was only 11.76%, but when the lactate levels increased by more than 80%, the ICU mortality rate was 65.38%. The extent by which the lactate level changed from the first measurement to the second measurement when the initial measurement was above 4.0 mmol/L greatly influenced whether a patient died. Figure 4-4 shows the trend of ICU mortality rates compared to percent change in lactate of admissions with any initial lactate levels.
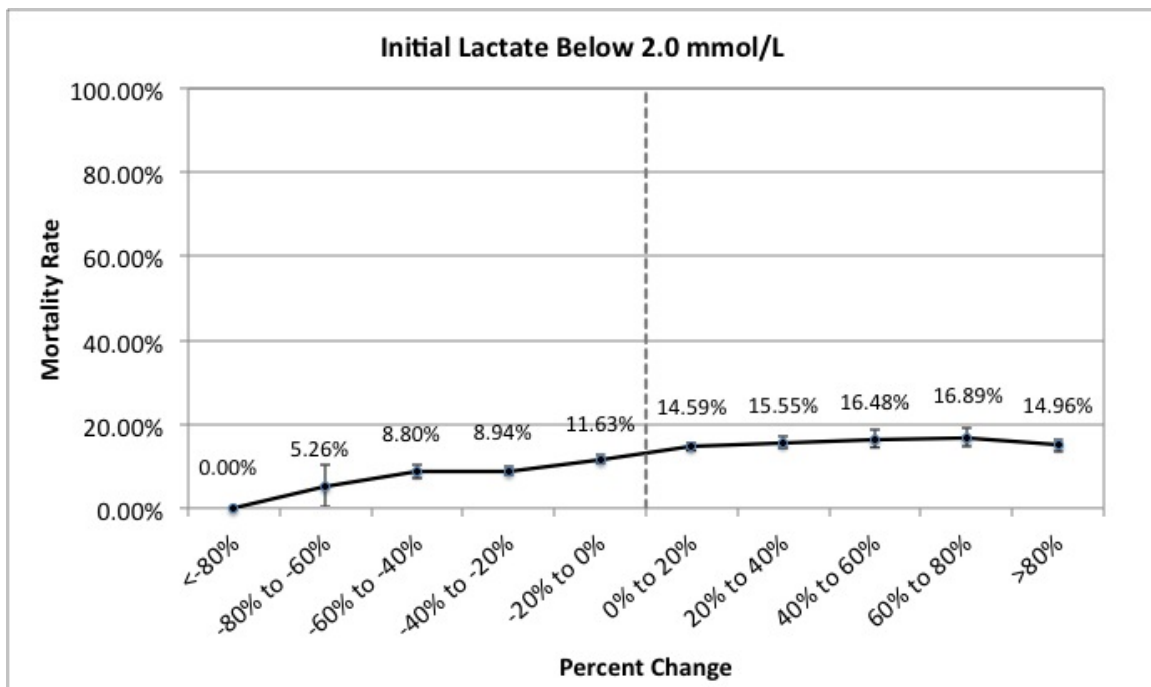
Figure 4-1: Percent Change in Lactate From First to Second Measurement Vs. ICU Mortality When the Initial Lactate Level Was Below 2.0 mmol/L
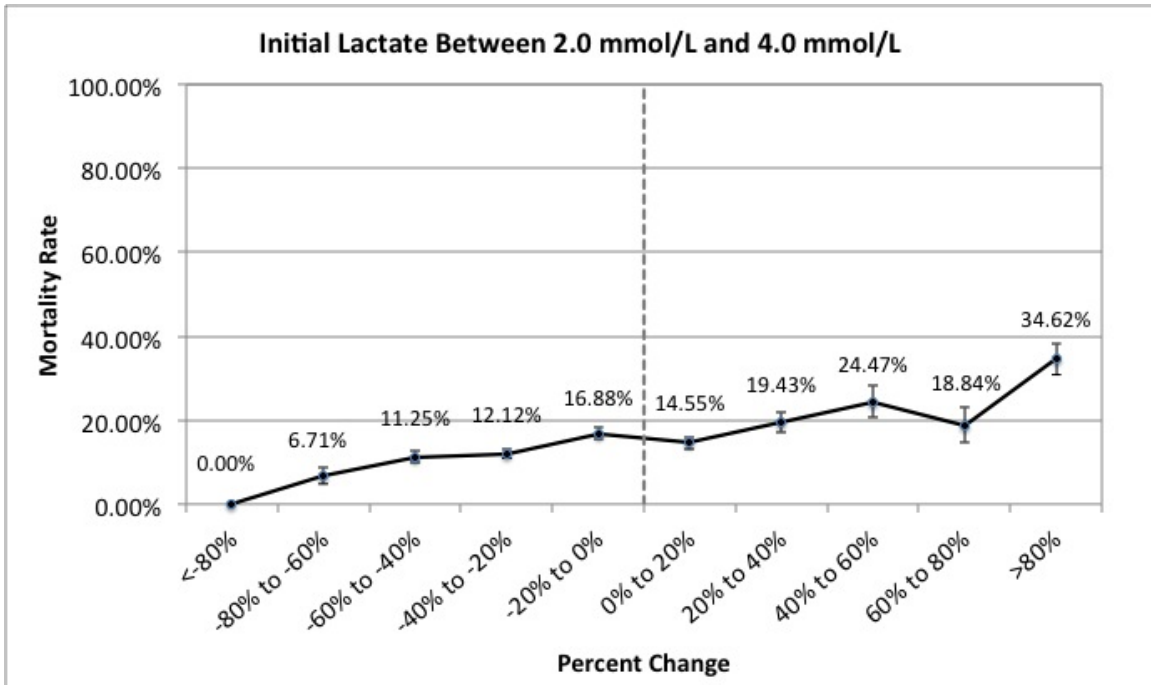
Figure 4-2: Percent Change in Lactate From First to Second Measurement Vs. ICU Mortality When the Initial Lactate Level Was Between 2.0 mmol/L and 4.0 mmol/L
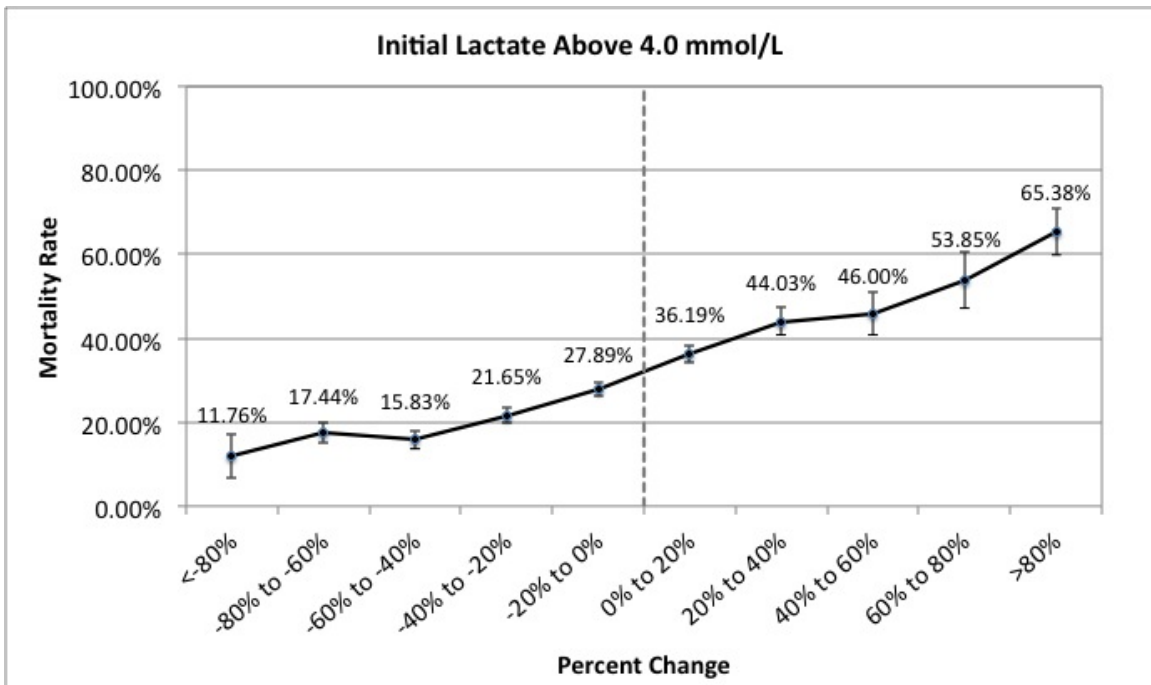
Figure 4-3: Percent Change in Lactate From First to Second Measurement Vs. ICU Mortality When the Initial Lactate Level Was Above 4.0 mmol/L
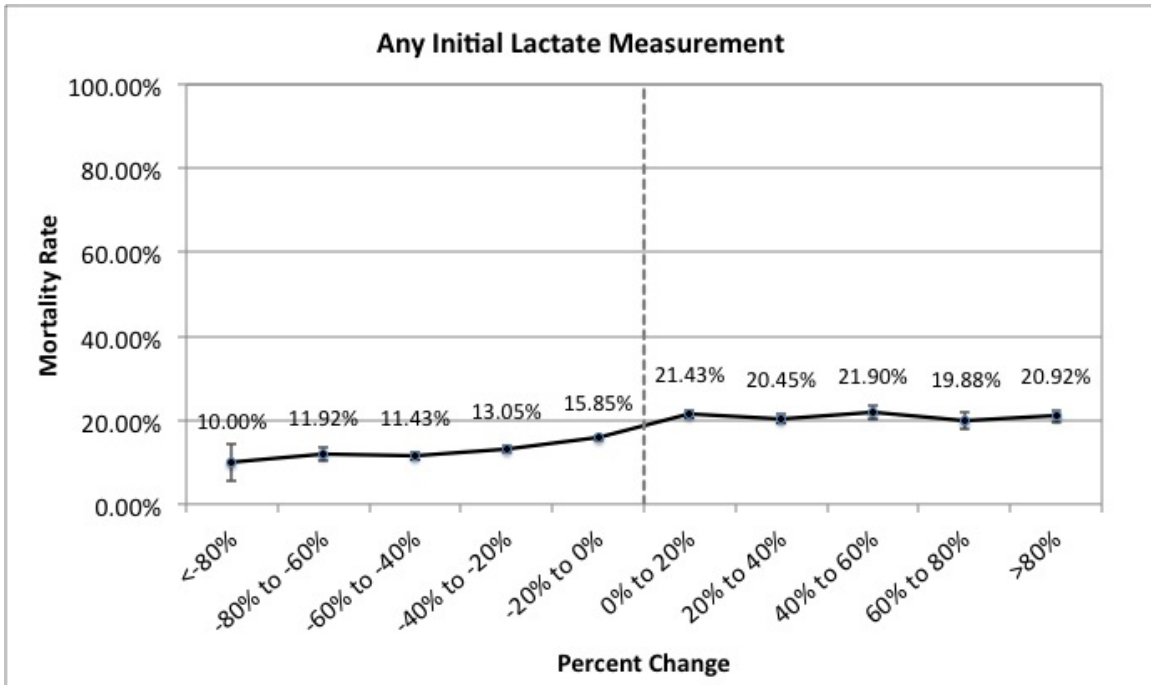
Figure 4-4: Percent Change in Lactate From First to Second Measurement Vs. ICU Mortality for All ICU Admissions with Any Lactate

4.2 Lactate Associations in Different Care Units

To further understand lactate associations in ICU patients, we looked at the ICU mortality, 30 day mortality, and length of stay in each individual care unit. There were 3980 admissions in the MICU with lactate measurements, 1771 in the FICU, 2590 in the CCU, 5149 in the CSRU, and 869 in the SICU. We were interested to determine if patients in a particular care unit had greater associations with lactate.

4.2.1 ICU Mortality

We looked at the ICU mortality rate of admissions with lactate measurements in each of the different care units. The ICU mortality rate of admissions with lactate measurements for each care unit are detailed in Table 4.5. The ICU mortality rates of each care unit were higher when only admissions with any lactate measurement were included. The ICU mortality rate including those with or without lactate measurements was 9.5% in the MICU, 8.1% in the FICU, 7.5% in the CCU, 4.7% in the

CSRU, and 6.0% in the SICU.

The ICU mortality rate was the lowest in the CSRU, most likely because cardiac surgery recovery patients are generally healthy before going into surgery. The cause for increased lactate during anesthesia, surgery, and by-pass is quickly resolvable as opposed to the causes of critical medical illnesses. The ICU mortality rate may also be lower for patients in the CSRU because there is a protocol in place that requires lactate measurements to be taken in the CSRU (at the hospital from which we get our patient data). The ICU mortality rate was the highest in the MICU most likely because patients in the MICU have underlying illnesses. Admissions with a lactate measurement on average must be sicker than those who do not get lactate measurements.

Table 4.5: ICU Mortality of Admissions With a Lactate Measurement in Each ICU Care Unit

	Died in the ICU	Did not Die in the ICU	Total Admissions	ICU Mortality Rate
MICU	704	3,276	3,980	17.7%
FICU	231	1,540	1,771	13.0%
CCU	420	2,170	2,590	16.2%
CSRU	438	4,711	5,149	8.5%
SICU	85	784	869	9.8%

4.2.2   30 Day Mortality

We looked at the 30 day mortality rate of admissions with lactate measurements in each care unit. The 30 day mortality rates of those with lactate measurements in each care unit are detailed in Table 4.6. The 30 day mortality rates of just patients with lactate measurements were much higher than the 30 day mortality rates of each

care unit when all patients were included. The 30 day mortality rate including those with or without lactate measurements was 21.6% in the MICU, 15.0% in the FICU, 15.3% in the CCU, 11.0% in the CSRU, and 11.9% in the SICU.

Table 4.6: 30 Day Mortality of Admissions With a Lactate Measurement in Each ICU Care Unit

	Died within 30 Days	Did not Die within 30 Days	Total Admissions	30 Day Mortality Rate
MICU	1,249	2,731	3,980	31.4%
FICU	360	1,411	1,771	20.3%
CCU	657	1,933	2,590	25.4%
CSRU	819	4,330	5,149	15.9%
SICU	142	727	869	16.3%

4.2.3   Length of Stay

The average and median length of stay for admissions with lactate measurements that did not die in the ICU was similar across all care units. The average and median lengths of stay for each care unit are summarized in Table 4.7.

4.3   Conditions Associated with High Lactate

We identified which conditions were most associated with high lactate levels. We found the primary ICD-9 codes of all ICU admissions with an initial lactate level greater than 4.0 mmol/L. The ten most frequent conditions were unspecified septicemia (38.9), coronary atherosclerosis of native coronary artery (414.01), subendocardial infarction initial episode of care (410.71), septicemia due to E. coli (38.42),

Table 4.7: Average and Median Length of Stay of Admissions With Lactate Levels Broken Down By Care Unit

	Average Length of Stay (Days)	Median Length of Stay (Days)
MICU	6.5	3.4
FICU	7.5	3.7
CCU	7.3	4.0
CSRU	6.1	3.1
SICU	5.5	2.8

acute respiratory failure (518.81), congestive heart failure unspecified (428), pneumonitis due to inhalation of food or vomitus (507), acute and subacute necrosis of liver (570), acute myocardial infarction of other anterior wall (410.11), and acute myocardial infarction of other inferior wall (410.41). The number of admissions with initial lactate levels above 4.0 mmol/L with one of the primary ICD-9 codes listed is shown in Table 4.8.

We found that the most common conditions associated with lactate can be broken in three categories: sepsis, cardiac conditions, and respiratory conditions. The condition most commonly associated with high lactate was sepsis, so we have further studied this population in the following chapter. Further research should be done on the other two populations of patients associated with high lactate levels. Even though these populations were the most common that we found, there were many different conditions that must be associated with high lactate. There were 2,240 admissions with high lactate levels, but the condition most associated with high lactate was only found as the primary condition in 333 admissions.

Table 4.8: Primary ICD-9 Codes Most Commonly Associated with High Lactate Levels (Of a Total of 2,240 Admissions With High Lactate Levels)

ICD-9 Code	Description	Number of Admissions
38.9, 38.42	unspecified septicemia, septicemia due to E. coli	333
410.11, 410.41, 410.71	acute myocardial infarction of other anterior/inferior wall, subendocardial infarction initial episode of care	129
414.01	coronary atherosclerosis of native coronary artery	89
518.81	acute respiratory failure	41
428	congestive heart failure unspecified	34
507	pneumonitis due to inhalation of food or vomitus	28
570	acute and subacute necrosis of liver	26

Chapter 5

Lactate Associations in Septic Patients

5.1 Martin Criteria Severe Sepsis

There were 3,958 ICU admissions which met the Martin criteria for severe sepsis. No lactate measurement was taken during 938 of these admissions (23.7%), whereas lactate measurements were taken during 3,021 of these admissions (76.3%).

5.1.1 ICU Mortality

Martin criteria severe sepsis admissions with no lactate measurement had a much lower ICU mortality rate of 8.5% compared to the 35.3% ICU mortality rate of admissions with a lactate measurement. Due to the 938 patients without any lactate measurements, the overall ICU mortality rate of all severely septic patients under Martin criteria was 21.5%. Table 5.1 summarizes the results in detail.

Notice in Table 5.1 that ICU mortality increased as the initial lactate level increased. Martin criteria severe sepsis admissions with lactate levels below 2.0 mmol/L had an 18.9% ICU mortality rate, compared to patients with initial lactate levels above 4.0 mmol/L which had a much larger ICU mortality rate of 46.6%.

Table 5.1: ICU Mortality Vs. Lactate for Martin Criteria Severe Sepsis Patients

	Died in the ICU	Did not Die in the ICU	Total ICU admissions	ICU Mortality Rate
Initial Lactate ≤ 2.0 mmol/L	296	1,272	1,568	18.9%
Initial Lactate > 2.0 mmol/L and < 4.0 mmol/L	221	646	867	25.5%
Initial Lactate ≥ 4.0 mmol/L	272	314	586	46.6%
Any Lactate Measurement	789	2,232	3021	35.3%
No Lactate Measurement	60	878	938	8.5%
All Sepsis Admissions	849	3,109	3,958	21.5%

5.1.2 30 Day Mortality

The 30 day morality rate of all severely septic patients identified with the Martin criteria was 36.2%. Admissions where no lactate was measured had a slightly lower 30 day mortality rate of 25.8%, and those where lactate was measured had a slightly higher 30 day mortality rate of 39.5%. Table 5.2 summarizes the 30 day mortality results.

Just as ICU mortality rate increased with increased lactate levels, so did the 30 day mortality rate. Severely septic patients with initial lactate levels below 2.0 mmol/L had a 30 day mortality rate of 31.6%, whereas admissions with lactate levels above 4.0 mmol/L had a very high 30 day mortality rate of 59.2%.

Table 5.2: 30-Day Mortality Vs. Lactate for Martin Criteria Severe Sepsis Patients

	Died within 30 Days	Did not Die within 30 Days	Total ICU admissions	30 Day Mortality Rate
Initial Lactate ≤ 2.0 mmol/L	496	1,072	1,568	31.6%
Initial Lactate > 2.0 mmol/L and < 4.0 mmol/L	350	517	867	40.4%
Initial Lactate ≥ 4.0 mmol/L	346	239	585	59.2%
Any Lactate Measurement	1,192	1,828	3,020	39.5%
No Lactate Measurement	242	696	938	25.8%
All Sepsis Admissions	1,434	2,524	3,958	36.2%

5.1.3   Length of Stay

The average and median length of stay of ICU survivors, 8.8 and 4.1 days respectively, was much longer than the average and median length of stay of all ICU admissions who survived, 5.4 and 2.0 days respectively. Those without lactate measurements had average and median lengths of stay of 5.0 and 2.1 days respectively, which was almost identical to the average and median length of stay of all ICU admissions who survived. Admissions that had a lactate measured had very high average and median lengths of stay that were 10.2 and 5.6 days, respectively. The length of stay results for Martin criteria sepsis patients who survived their ICU stay are summarized in Table 5.3.

The average and median length of stay of Martin criteria severe sepsis patients who survived their ICU stay increased as the initial lactate measurement increased.

Those with low lactate levels had an average length of stay of 9.7 days and a median length of stay of 5.2 days, whereas those with very high lactate levels stayed in the ICU for an average of 11.5 days and a median of 7.6 days.

Table 5.3: Average and Median Length of Stay for Sepsis Admissions Defined by Martin Criteria Who Survived Their ICU Stay

	Average Length of Stay (Days)	**Median Length of Stay (Days)**
Initial Lactate ≤ 2.0 mmol/L	9.7	5.2
Initial Lactate >2.0 mmol/L and <4.0 mmol/L	10.6	5.6
Initial Lactate ≥ 4.0 mmol/L	11.5	7.6
Any Lactate Measurement	10.2	5.6
No Lactate Measurement	5.0	2.1
All Sepsis Admissions	8.8	4.1

5.1.4   Severity of Illness

The average SOFA score and the average SAPS I score both increased as the initial level of lactate increased. Admissions with any lactate measurement had much higher scores on average than admissions without a lactate measurement. Martin criteria severe sepsis admissions with any lactate level had an average SOFA score of 9.04 and the average SAPS I score of 17.33. Admissions with lactate below 2.0 mmol/L had average SOFA score of 7.69 and SAPS I score of 15.94. There was a large increase in average severity scores in admissions with very high lactate levels greater than 4.0

mmol/L. The average SOFA score was 12.02 and the average SAPS I score was 20.75. The severity score results are summarized in Table 5.4.

Table 5.4: Average SOFA and SAPS I Scores Sepsis Admissions Defined by Martin Criteria

	Average SOFA Score	**Average SAPS I Score**
Initial Lactate ≤ 2.0 mmol/L	7.69	15.94
Initial Lactate >2.0 mmol/L and <4.0 mmol/L	9.49	17.57
Initial Lactate ≥ 4.0 mmol/L	12.02	20.75
Any Lactate Measurement	9.04	17.33
No Lactate Measurement	5.31	12.96
All Sepsis Admissions	8.20	16.44

5.1.5 Change in Lactate

The ICU mortality rate of Martin criteria severe sepsis admissions with initial lactate greater than 4.0 mmol/L was much lower when the lactate decreased from the first to the second measurement than when the lactate increased, as shown in Figure 5-1. When lactate decreased by more than 80%, the mortality rate was 28.57%. When lactate increased by 40 to 60%, the mortality rate was very high at 76.47%. The mortality rate was lower when lactate increased by more than 80%, but this was mostly likely due to the small sample size of admissions with initial lactate levels above 4.0 mmol/L and increasing by more than 80%. Overall, the mortality rate was much larger when lactate increased.

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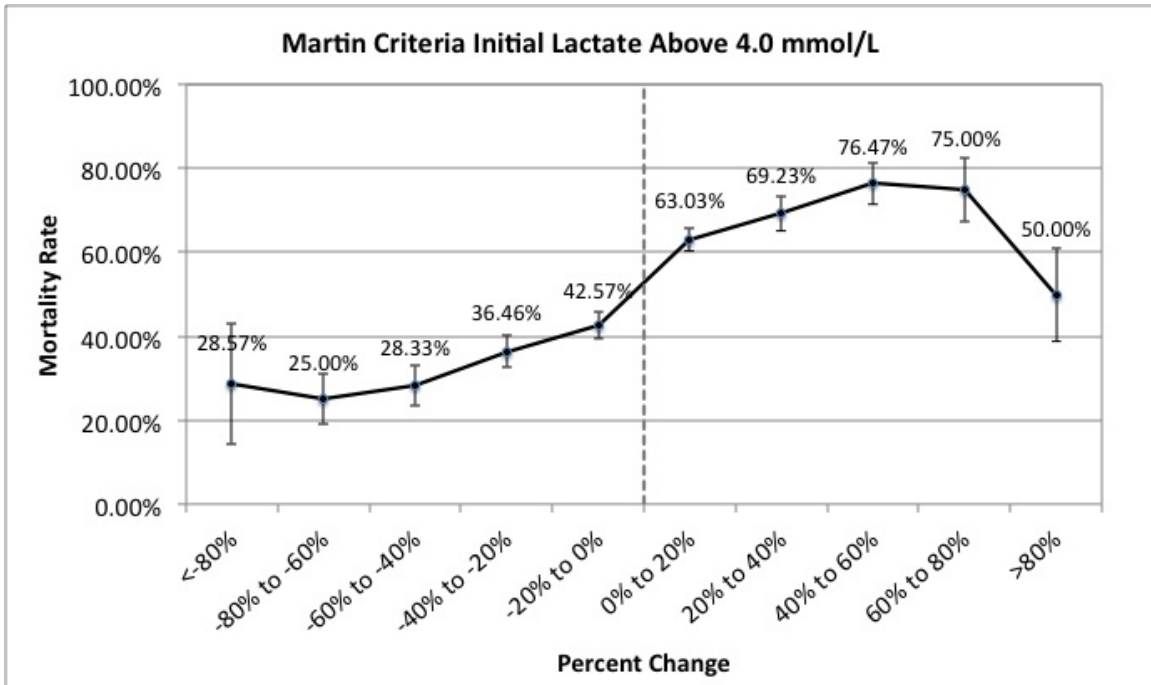
Figure 5-1: Percent Change in Lactate From First to Second Measurement Vs. ICU Mortality When the Initial Lactate Level Was Above 4.0 mmol/L for Sepsis Admissions Defined by Martin Criteria

5.2 Angus Criteria Severe Sepsis

We identified 6,362 admissions that met the Angus criteria for severe sepsis. Of these admissions, 4,320 had lactate levels (67.9%) and 2,043 did not have lactate levels (32.1%). We found more patients with severe sepsis using the Angus criteria than we found using the Martin criteria because the Angus criteria are less stringent.

5.2.1 ICU Mortality

The ICU mortality rate of all admissions identified using the Angus criteria for severe sepsis was 16.9%. Admissions with a lactate level had a mortality rate of 22.5%, whereas admissions without a lactate level had a much lower mortality rate of 5.1%. Those without lactate levels seem to be less ill on average than those with lactate levels.

The mortality rate increased as the initial lactate level increased. The ICU mortality rate of admissions with initial lactate less than 2.0 mmol/L was 16.8%, whereas

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the ICU mortality of admissions with initial lactate greater than 4.0 mmol/L was 39.5%. These results are detailed in Table 5.5.

Table 5.5: ICU Mortality Vs. Lactate for Sepsis Admissions Defined by Angus Criteria

	Died in the ICU	Did not Die in the ICU	Total ICU admissions	ICU Mortality Rate
Initial Lactate ≤ 2.0 mmol/L	396	1,967	2,363	16.8%
Initial Lactate > 2.0 mmol/L and < 4.0 mmol/L	263	906	1169	22.5%
Initial Lactate ≥ 4.0 mmol/L	312	476	788	39.5%
Any Lactate Measurement	971	3,349	4,320	22.5%
No Lactate Measurement	104	1939	2,043	5.1%
All Sepsis Admissions	1,075	5,288	6,362	16.9%

5.2.2   30 Day Mortality

The 30 day mortality rate of all admissions identified by the Angus criteria for severe sepsis was 30.0%. Admissions with a lactate measurement had a slightly higher 30 day mortality rate of 34.5%, whereas those without a lactate measurement had a lower 30 day mortality rate of 20.4%.

The 30 day mortality rate of admissions with high lactate levels above 4.0 mmol/L, 53.3%, was much higher than the 30 day mortality rate of admissions with low lactate below 2.0 mmol/L, 27.6%. Details for 30 day mortality are located in Table 5.6.

Table 5.6: 30-Day Mortality Vs. Lactate for Sepsis Admissions Defined by Angus Criteria

	Died within 30 Days	Did not Die within 30 Days	Total ICU admissions	30 Day Mortality Rate
Initial Lactate ≤ 2.0 mmol/L	653	1,710	2,363	27.6%
Initial Lactate > 2.0 mmol/L and < 4.0 mmol/L	419	750	1169	35.8%
Initial Lactate ≥ 4.0 mmol/L	420	368	788	53.3%
Any Lactate Measurement	1,492	2,828	4,320	34.5%
No Lactate Measurement	416	1,627	2,043	20.4%
All Sepsis Admissions	1,908	4,455	6,363	30.0%

5.2.3 Length of Stay

The average and median length of stay of all Angus criteria sepsis admissions that did not die while in the ICU was 7.1 days and 3.5 days, respectively. The admissions that had a lactate level had an average length of stay of 9.3 days and a median length of stay of 5.1 days. Admissions without a lactate level had a much shorter length of stay on average. Admissions without lactate levels had an average length of stay of 3.1 days and a median length of stay of 2.0 days.

The length of stay was longer for admissions with higher initial lactate levels. Admissions with lactate levels below 2.0 mmol/L had an average length of stay of 8.9 days and a median of 4.8 days. Admissions with high lactate above 4.0 mmol/L had a longer average length of stay of 10.9 days and a median of 6.9 days. The results are

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summarized in Table 5.7.

Table 5.7: Average and Median Length of Stay Vs. Lactate for Sepsis Admissions Defined by the Angus Criteria Who Survived Their ICU Stay

	Average Length of Stay (Days)	Median Length of Stay (Days)
Initial Lactate ≤ 2.0 mmol/L	8.9	4.8
Initial Lactate >2.0 mmol/L and <4.0 mmol/L	9.5	5.0
Initial Lactate ≥ 4.0 mmol/L	10.9	6.9
Any Lactate Measurement	9.3	5.1
No Lactate Measurement	3.1	2.0
All Sepsis Admissions	7.1	3.5

5.2.4 Severity of Illness

The average SOFA score and average SAPS I score of all severely septic patients identified using the Angus criteria that had lactate levels were 8.60 and 16.96, respectively. Admissions with any lactate measurement had higher severity scores on average than admissions without a lactate measurement. The severity of illness increased as the initial lactate level increased. Admissions with initial lactate less than 2.0 mmol/L had an average SOFA score of 7.40 and an average SAPS I score of 15.70. Admissions with high lactate above than 4.0 mmol/L had the highest average SOFA score of 11.62 and the highest average SAPS I score of 20.40. These results are summarized in Table 5.8.

Table 5.8: Average SOFA and SAPS I Scores Vs. Lactate for Sepsis Admissions Defined by Angus Criteria

	Average SOFA Score	Average SAPS I Score
Initial Lactate ≤ 2.0 mmol/L	7.40	15.70
Initial Lactate >2.0 mmol/L and <4.0 mmol/L	8.98	17.21
Initial Lactate ≥ 4.0 mmol/L	11.62	20.40
Any Lactate Measurement	8.60	16.96
No Lactate Measurement	4.73	12.54
All Sepsis Admissions	7.38	15.66

5.2.5 Change in Lactate

The ICU mortality rate of Angus criteria severe sepsis admissions with initial lactate greater than 4.0 mmol/L was much lower when the lactate decreased from the first to the second measurement than when the lactate increased, as shown in figure 5-2. Although the ICU mortality rate is not strictly increasing with increased percent change in lactate, the overall trend is increasing. When lactate decreased by more than 80%, the ICU mortality rate was very low at 9.09%. When lactate increased by 60 to 80%, the ICU mortality rate was the highest at 77.78%. Overall, the mortality rate was much larger when lactate levels increased.
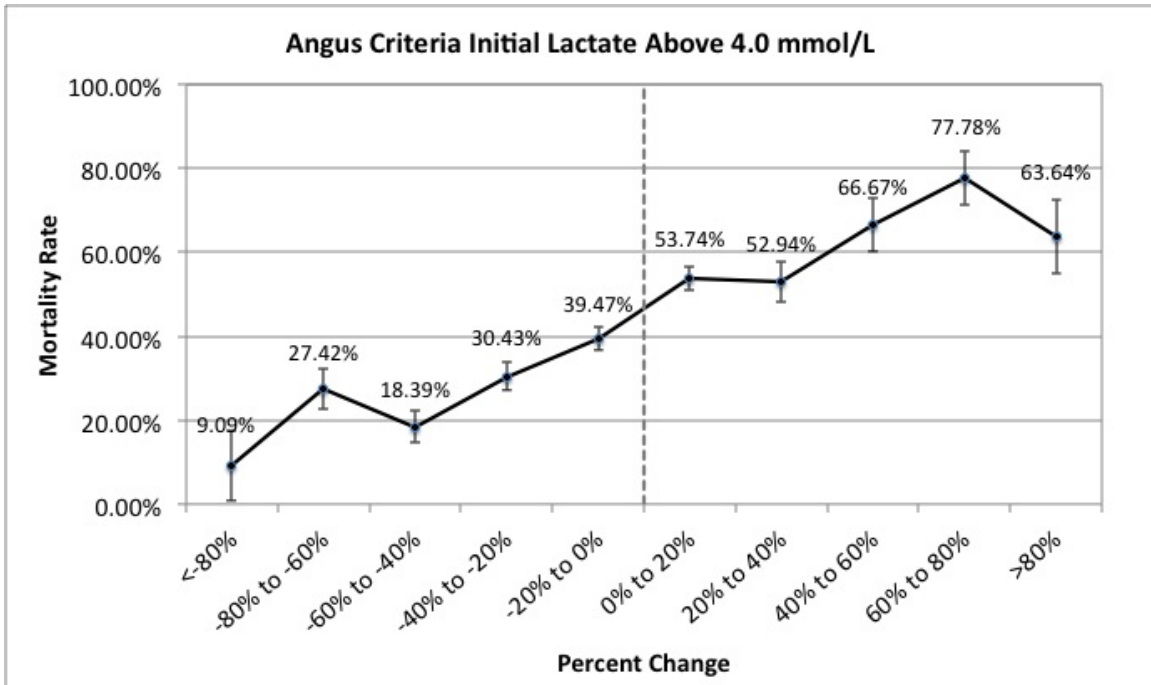
Figure 5-2: Percent Change in Lactate From First to Second Measurement Vs. ICU Mortality When the Initial Lactate Level Was Above 4.0 mmol/L for Sepsis Patients Defined by Angus Criteria

5.3 Infection and SIRS Criteria Sepsis

There were 9,911 ICU admissions identified as septic on the first day of admission, using the criteria of having an infection and SIRS, as described in section 3.6.3. Of these admissions, 6,032 had lactate measurements on the first day of their admission (60.9%) whereas 3,879 admissions did not (39.1%).

5.3.1 ICU Mortality

Admissions that were identified as septic on the first day using the infection and SIRS criteria had an overall ICU mortality rate of 11.7%. The ICU mortality rate of admissions with lactate levels was higher (15.1%), and the ICU mortality rate of those without lactate levels was much lower (6.3%).

The ICU mortality rate of admissions with initial lactate levels measured on the first day below 4.0 mmol/L was low. Admissions initial lactate below 2.0 mmol/L had an ICU mortality rate of 10.9%, and admissions with initial lactate level between

2.0 mmol/L and 4.0 mmol/L had an ICU mortality rate of 12.9%. Admissions with initial lactate greater than 4.0 mmol/L had a much higher ICU mortality rate of 30.2%. These results are detailed in Table 5.9.

Table 5.9: ICU Mortality Vs. Lactate for Sepsis Patients Defined by Infection and SIRS Criteria

	Died in the ICU	Did not Die in the ICU	Total ICU admissions	ICU Mortality Rate
Initial Lactate ≤ 2.0 mmol/L	333	2,732	3,065	10.9%
Initial Lactate > 2.0 mmol/L and < 4.0 mmol/L	236	1,601	1,837	12.9%
Initial Lactate ≥ 4.0 mmol/L	341	789	1,130	30.2%
Any Lactate Measurement	910	5,122	6,032	15.1%
No Lactate Measurement	246	3,633	3,879	6.3%
All Sepsis Admissions	1,156	8,755	9,911	11.7%

5.3.2   30 Day Mortality

The overall 30 day mortality rate of sepsis admissions found using the infection and SIRS criteria was 21.2%. Admissions without a lactate measurement on the first day of admission had a 30 day mortality rate of 15.3%, whereas those with a lactate measurement on the first day had a 30 day mortality rate of 25.1%.

The 30 day mortality rate for admissions with lactate below 4.0 mmol/L was much smaller than the 30 day mortality rate for admissions with lactate above 4.0 mmol/L.

Admissions with initial lactate less than 2.0 mmol/L had a 30 day mortality rate of 19.8%, and admissions with initial lactate between 2.0 mmol/L and 4.0 mmol/L had a 30 day mortality rate of 22.8%. Admissions with lactate above 4.0 mmol/L had a high 30 day mortality rate of 42.9%. Details of these results are found in Table 5.10.

Table 5.10: 30 Day Mortality Vs. Lactate for Sepsis Patients Defined by Infection and SIRS

	Died within 30 Days	Did not Die within 30 Days	Total ICU admissions	30 Day Mortality Rate
Initial Lactate ≤ 2.0 mmol/L	607	2,458	3,065	19.8%
Initial Lactate > 2.0 mmol/L and < 4.0 mmol/L	419	1,418	1,837	22.8%
Initial Lactate ≥ 4.0 mmol/L	485	645	1,130	42.9%
Any Lactate Measurement	1,511	4,521	6,032	25.1%
No Lactate Measurement	594	3,285	3,879	15.3%
All Sepsis Admissions	2,105	7,806	9,911	21.2%

5.3.3 Length of Stay

The average and median length of stay of all sepsis admissions defined by infection and SIRS on the first day that did not die while in the ICU was 5.4 days and 2.9 days, respectively. The admissions with a lactate level had an average length of stay was 6.5 days and a median length of stay was 3.4 days. The admissions without a lactate level had a much shorter length of stay on average. Those without lactate levels had

an average length of stay was 3.9 days and a median length of stay of 2.3 days.

The length of stay was slightly longer for admissions with higher initial lactate levels. Admissions with lactate levels below 2.0 mmol/L had an average length of stay of 6.0 days and a median of 3.2 days, whereas admissions with high lactate above 4.0 mmol/L had a longer average length of stay of 7.7 days and a median of 4.5 days. The results are summarized in Table 5.11.

Table 5.11: Average and Median Length of Stay for Sepsis Admissions Defined by Infection and SIRS Who Survived Their ICU Stay

	Average Length of Stay (Days)	Median Length of Stay (Days)
Initial Lactate $\leq$ 2.0 mmol/L	6.0	3.2
Initial Lactate >2.0 mmol/L and <4.0 mmol/L	6.7	3.3
Initial Lactate $\geq$ 4.0 mmol/L	7.7	4.5
Any Lactate Measurement	6.5	3.4
No Lactate Measurement	3.9	2.3
All Sepsis Admissions	5.4	2.9

5.3.4   Severity of Illness

The average SOFA score and average SAPS I score of all septic patients defined by infection and SIRS with lactate levels were 8.42 and 16.8, respectively. Admissions with any lactate measurement on the first day of admission had higher severity scores on average than admissions that did not have a lactate measurement on the first day.

The severity of illness increased as the initial lactate level increased. Admissions with initial lactate less than 2.0 mmol/L had an average SOFA score of 7.4 and an average SAPS I score of 15.79. Admissions with high lactate above than 4.0 mmol/L had the highest average SOFA score of 11.18 and the highest average SAPS I score of 19.88. These results are summarized in Table 5.12.

Table 5.12: Average SOFA and SAPS I Scores Vs. Lactate for Sepsis Admissions Defined by Infection and SIRS Criteria

	Average SOFA Score	Average SAPS I Score
Initial Lactate ≤ 2.0 mmol/L	7.4	15.79
Initial Lactate >2.0 mmol/L and <4.0 mmol/L	8.64	16.83
Initial Lactate ≥ 4.0 mmol/L	11.18	19.88
Any Lactate Measurement	8.42	16.8
No Lactate Measurement	5.85	13.94
All Sepsis Admissions	7.51	15.78

5.3.5 Change in Lactate

The ICU mortality rate of sepsis admissions, defined by infection and SIRS criteria, with initial lactate greater than 4.0 mmol/L was much lower when the lactate decreased from the first to the second measurement than when the lactate increased, as shown in figure 5-3. When lactate decreased by more than 80%, the ICU mortality rate was only 5.00%. When lactate increased by more than 80%, the ICU mortality rate was the highest at 71.43%. The ICU mortality rate had a large dip when lactate
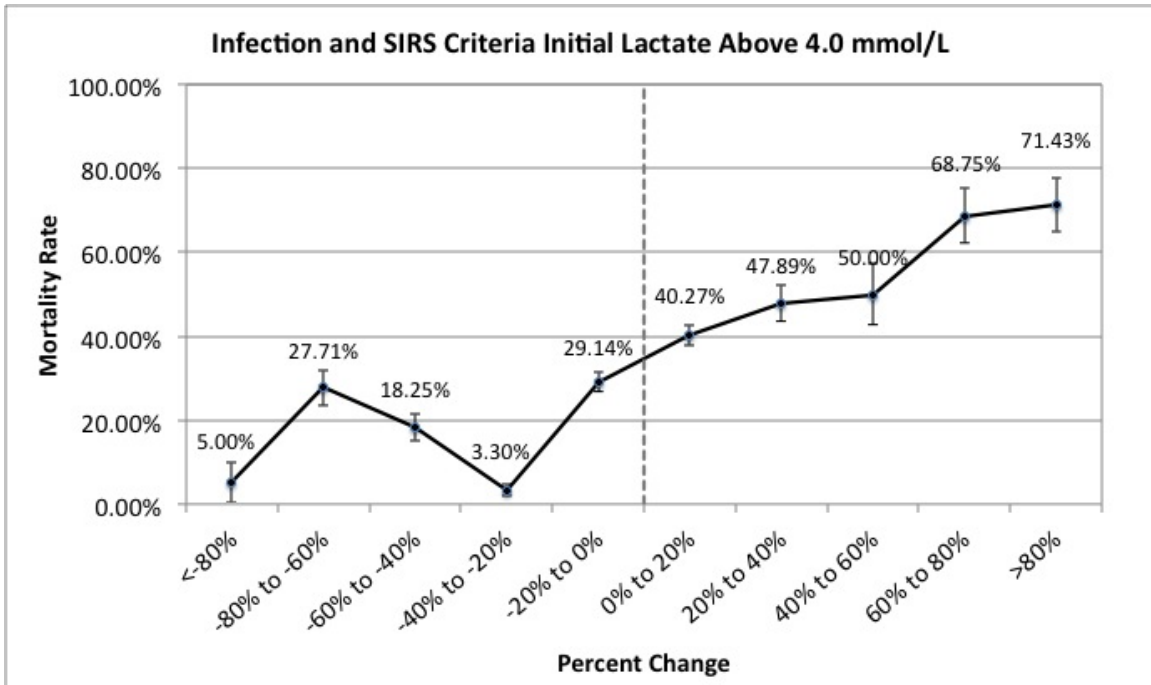
Figure 5-3: Percent Change in Lactate From First to Second Measurement Vs. ICU Mortality When the Initial Lactate Level Was Above 4.0 mmol/L for Sepsis Admissions Defined by Infection and SIRS Criteria

decreased by 20 to 40% due to the small sample size of patients with initial lactate above 4.0 mmol/L whose lactate decreased by 20 to 40%. Overall, the ICU mortality rate trend increased as the change in lactate increased from the first measurement to the second measurement.

Chapter 6

Discussion

6.1 All ICU Admissions

We concluded that on average patients with high initial lactate levels were sicker than those with low lactate levels. Patients with high initial lactate levels above 4.0 mmol/L had a much higher ICU mortality rate and 30 day mortality rate than patients with normal lactate levels below 2.0 mmol/L. The ICU mortality rate and 30 day mortality rate for patients with high lactate levels were more than double the ICU and 30 day mortality rates of patients with normal lactate levels. The average length of stay of ICU survivors, a surrogate variable we used for how sick a patient was, was a little longer for patients with high lactate than for patients with low lactate. Admissions with high lactate typically were sicker, had longer ICU stays, and were more likely to have poor outcomes.

To support our conclusions that patients with high initial lactate were sicker on average than those with low initial lactate, we looked at average severity scores of these populations. Admissions with low initial lactate had on average lower SOFA scores and lower SAPS I scores than admissions with high initial lactate. A higher severity score indicates that an illness is more severe and there is a greater likelihood of a poor outcome. Patients with higher initial lactate had higher severity scores which supported our original conclusion that in general patients with very high initial lactate levels had worse outcomes and were sicker than patients with low initial lactate levels.

We also concluded that patients who do not get lactate levels measured are less sick on average than patients who do get lactate levels measured. The ICU mortality rate and 30 day mortality rate of patients without lactate measurements were less than half of what the ICU mortality rate and 30 day mortality rate were for all ICU admissions in our cohort. We also saw that patients without lactate measured had a much shorter length of stay on average than patients with lactate measurements. In general, we concluded that patients who were less sick in the ICU did not get a lactate measurement, most likely because their physicians did not think the patients' lactate levels would be out of the normal range or need to be addressed. Those without lactate measured who died in the ICU may have died quickly before any lactate could be measured. Further studies would need to be done to confirm this hypothesis.

Looking at the admissions with lactate measurements in each care unit did not give us much additional information. The ICU mortality rates of admissions with lactate measurements in each care unit were slightly higher than the ICU mortality rates of all patients in each care unit. The 30 day mortality rates in each care unit followed the same trend. The same trend held for the average lengths of stay in each care unit as well.

6.2   Septic Admissions

We concluded that admissions that were classified as septic or severely septic and that had high initial lactate levels were typically sicker than admissions that were septic with low initial lactate levels, the same trend we saw in all ICU patients. In all three septic cohorts we studied, the ICU mortality rate and 30 day mortality rate increased as the initial lactate level increased. The ICU mortality rate of admissions with initial lactate levels above 4.0 mmol/L was more than double the ICU mortality rate of admissions with initial lactate levels below 2.0 mmol/L in all three septic cohorts. In addition, the 30 day mortality rates for admissions with high initial lactate were almost twice as high as the 30 day mortality rates of admissions with low initial lactate levels. Outcomes were especially poor for severe sepsis patients defined by the

Martin criteria; the 30 day mortality rate reached almost 60% for admissions with high initial levels.

The average lengths of stay associated with each range of initial levels also showed that on average septic patients with high lactate were sicker than septic patients with low lactate. All of the septic cohorts showed the same trend; the higher the initial lactate level, the longer the length of stay. A longer length of stay suggests that the patients were sicker and needed attention for longer.

We investigated our conclusions about severity of illness in septic patients with high lactate by looking at average SAPS I and SOFA scores. In all three septic cohorts, we saw much higher average severity scores, indicating higher severity of illness, in patients with high initial lactate compared to the average scores of patients with low initial lactate. The average severity scores we found support our findings that septic patients with high lactate are usually sicker than patients with low lactate.

6.3 Change in Lactate

Our results showed that change in lactate level is also very useful in predicting outcome, along with initial lactate level. We looked at change in lactate between the first and second measurement in combination with the initial lactate level to gain an even better understanding of the predictive value of lactate changes. We found that looking at just lactate change by itself in all ICU patients did not show a large difference in the ICU mortality rates. In all ICU admissions with two or more lactate measurements, lactate levels that increased from the first to the second measurement had a slightly higher mortality rate than admissions with lactate levels that decreased. Looking at lactate change along with initial lactate level presented a much stronger trend. ICU admissions that started with high lactate levels which increased had a much higher mortality rate than those with high lactate levels that decreased.

In septic admissions, we saw an even greater effect of lactate change on ICU mortality rates. There was a large increase in ICU mortality rates of septic admissions when the initial lactate was high and the second measurement was higher than the

first. ICU mortality rates reached over 70% for all septic cohorts when initial lactate was high and increased by a large amount, whereas ICU mortality rates were under 40% when the initial measurement was high but decreased. Knowing both the initial lactate measurement and change in lactate has much more predictive value than either measurement by itself, especially in septic patients.

It is still unknown why some admissions with high lactate that increases die while others live. It is also unknown why some admissions with low initial lactate that decreases die while others live. Further research is needed to understand the full predictive value of initial lactate combined with lactate clearance.

During this study, we did not control for the time between the first and second lactate measurements. There may be some admissions where the lactate was measured very frequently, while others may have had days in between measurements. Looking at the rate of change, as opposed to the just the percent change in lactate, may give more information about how lactate change is associated with ICU mortality.

6.4   Comparisons Across Cohorts

Admissions within the septic cohorts typically had worse outcomes than admissions in the total ICU cohort.The ICU mortality rates and 30 day mortality rates found for each of the defined septic cohorts overall were higher than the ICU mortality rates and 30 day mortality rates of the general ICU cohort. When including all patients with or without a lactate measurement, Martin criteria severe septic admissions had the highest ICU mortality rate overall, followed by the Angus criteria severe sepsis admissions. Septic patients defined by infection and SIRS had a lower ICU mortality rate than the other septic cohorts, but a slightly higher ICU mortality rate than all ICU admissions. The same trend is seen in the 30 day mortality rates of each cohort.

The ICU mortality rate and 30 day mortality rate of admissions with high lactate also vastly differed among the cohorts. The ICU mortality rate of Martin criteria severe sepsis patients with high initial lactate (46.4%) was much higher than the ICU mortality rates of patients with high initial lactate in the other cohorts. The next

highest ICU mortality rate associated with high initial lactate was 39.5%, which was for patients in the Angus criteria defined cohort. After that, there was the infection and SIRS defined septic cohort with an ICU mortality rate of 30.2%, and finally after that was all ICU admissions with an ICU mortality rate of only 26.8%. The 30 day mortality rates follow the same decreasing trend from 59.2% (Martin criteria admissions) to 41.6% (all ICU admissions). We concluded that patients identified with the Martin criteria had the most severe illnesses, and that the Angus criteria patients were a close second. It makes sense that these two cohorts were more ill than the septic patients identified with infection and SIRS because Angus and Martin criteria identify severe sepsis patients rather than just sepsis patients.

Although we saw large differences in mortality rates between the different cohorts, we did not see large differences in severity scores. Septic patients had slightly higher SOFA and SAPS I scores on average than all ICU admissions. All Martin criteria patients with a lactate measured had an average SOFA score of 9.04 and an average SAPS I score of 17.33, whereas the average SOFA and SAPS I scores of all ICU admissions with a lactate level, 7.41 and 15.91 respectively, were only somewhat lower. The average scores of the Angus criteria admissions and infection and SIRS criteria admissions were in between as expected.

The average severity scores were much higher for patients with lactate above 4.0 mmol/L, but again we didn't see a large difference across cohorts. The SOFA scores ranged from 10.1 to 12.0 (all ICU admissions to Martin admissions) and the SAPS I scores ranged from 19.2 to 20.8. The average severity scores of the three septic cohorts differed by less than one point, when including the entire population and when including just admissions with high initial lactate. Although we saw much different ICU mortality rates and 30 day mortality rates across the cohorts, there were not large differences in severity of illness based on severity scores. This shows that lactate levels may give information about severity of illness in addition to the information given by severity scores. Re-doing our methods but controlling for severity score may give interesting results about how much additional information lactate levels can give us about the severity of illness of a patient.

Chapter 7

Conclusion

7.1 Summary

In this thesis, we investigated the relationship between initial lactate levels and various easily measured parameters in ICU patients using the MIMIC II (version 2.6) database. We found that increased lactate levels were associated with a higher ICU mortality, higher 30 day mortality, longer ICU length of stay, and higher severity scores.

In addition to looking at the ICU population as a whole, we identified sepsis patients using three different criteria (Martin, Angus, and infection and SIRS) and studied their lactate levels. We found higher ICU mortality rates, higher 30 day mortality rates, longer lengths of stay, and higher severity scores in sepsis patients compared to those of all ICU patients. Sepsis patients with high initial lactate levels were the most severely ill of all the patients populations we investigated.

Of the three sepsis cohorts, the patients identified by the Martin criteria who had high lactate levels had the worst outcomes. The patients identified by the Angus criteria with high lactate had worse outcomes than the patients identified by infection and SIRS criteria who had high lactate. Although we saw very large differences in mortality rates, we did not see large differences in severity scores across the three cohorts. This suggests that knowing initial lactate levels may add predictive value in addition to severity scores. Lactate information may be important in addition to

classical severity scores in defining cohorts of patients.

We also investigated the relationship between initial lactate, change in lactate from the first measurement to the second measurement, and ICU mortality. We found that patients with high initial lactate levels in combination with an increase in lactate level typically had poorer outcomes than patients with high initial lactate levels with a decrease in lactate level.

7.2   Future Research Directions

There are a few different ways to further extend the research described in this thesis. One interesting possibility would be to explore the role of lactate in additional sub-populations of ICU patients. In addition to sepsis patients, we found that patients with cardiac problems and respiratory problems were two groups of patients that might be at high risk for elevated lactate levels. In the future, we could define new cohorts consisting of patients with respiratory or cardiac conditions and follow the same methods that were presented in this thesis in order to learn more about the role lactate in sub-populations of ICU patients.

Another possibility for future research would be to look more closely at the initial lactate measurements and change in lactate. Some patients start out with very high lactate levels and their lactate levels increase, but they still survive their ICU stay despite this. Looking at other common factors associated with these patients such as age, gender, and components of different severity scores may give light to why some survive while others do not. We saw very low mortality rates in patients with normal lactate whose lactate decreases, but there are still some patients that die. Identifying why some live while others die would be another question to solve. Being able to predict mortality using lactate measurements in combination with other features would be very useful to ICU doctors.

Following our methods again, but controlling for severity scores, is another idea for the future. Severity scores give a lot of information about how likely it is that a patient will die. Lactate measurements are not included in calculating the SOFA and

SAPS I scores, but lactate may give additional information about what a patient's outcome may be. Controlling for these scores would give us the ability to quantify how much predictive value knowing lactate measurements adds.

One final future research plan is to re-run our methods and analysis on a much larger cohort of patients to see if we obtain the same results. Our lab has recently gained access to a database of 2.6 million patients and is in the process of adding their information to the MIMIC II database (version 3). The patients are from many different hospitals, so analyzing the new data would eliminate any bias that may have been introduced in our current cohort, which is comprised of patients from only one hospital.

Appendix A

A.1   Antibiotics used in Sepsis Definition

The antibiotics used to signify infection in septic patients were: ampicillin-sulbactam, amoxicillin-clavulanic, amikacin, augmentin suspension, azithromycin, aztreonam, bactrim, cefepime, cefixime, cefotaxime, cefotetan, cefoxitin, cefpodoxime, ceftazidime, cefuroxime, ciprofloxacin, clarithromycin, clindamycin, colistin, daptomycin, doxycycline, ertapenem, erythromycin, gatifloxacin, gentamicin, imipenem, levofloxacin, linezolid, meropenem, metronidazole, minocycline, moxifloxacin, piperacillin, quinupristin, synercid, tetracycline, tigecycline, timentin, tobramycin, trimethoprim, unasyn, and vancomycin.

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