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Prediction of Septic Shock in Patients with Hematologic Malignancies

A thesis submitted in partial satisfaction of the requirements for the degree Master of

Science in Clinical Research

by

Scott B. Hu

2013

ABSTRACT OF THE THESIS

Prediction of Septic Shock in Patients with Hematologic Malignancies

by

Scott B. Hu

Master of Science in Clinical Research

University of California, Los Angeles, 2013

Professor Robert M. Elashoff, Chair

Delayed identification and treatment of septic shock is associated with increased

mortality. A retrospective chart review was performed on patients admitted with

hematologic malignancies in 2010 (188 control patients and 7 patients that developed

septic shock). A mixed effects multivariate logistic regression model was used to

determine if typical clinical biomarkers (vitals signs and routine laboratory studies) could

be used to predict the development of septic shock in patients with hematologic

malignancies prior to transfer to the intensive care unit. While routine vital signs could be

used to differentiate control patients from patients that developed septic shock even at 4

hours prior to intensive care transfer (AUC of 0.967), routine laboratory studies

performed significantly worse (AUC of 0.761).

The thesis of Scott B. Hu is approved.

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2013

Table of Contents

List of Figures

List of Tables

Acknowledgments

Introduction

Sepsis, a clinical syndrome characterized by multiple physiologic derangements in response to infection, is a common disease and a leading cause of death in the United States and worldwide. In a large U.S. epidemiologic study on a 1995 cohort based upon 7 large states, the incidence of severe sepsis was estimated at 751,000 cases, with estimates projected at 934,000 in 2010 and 1,110,000 in 2020[1]. Despite advances in supportive care, mortality rates in the United States range from 20% to 50%, with delays in diagnosis associated with decreased survival. While the definition of sepsis involves the presence of systemic inflammatory response syndrome (temperature, heart rate, respiratory rate, white blood cell count) and evidence of infection, there have been few studies looking at the prediction of the development of sepsis in patients in the hospital. Given that delayed identification of septic patients and intensive care unit (ICU) transfers are associated with increased mortality[2-4], early recognition of patients at risk for developing septic shock is imperative. .

Clinicians and medical staff fail to recognize patients with sepsis for a variety of reasons. First, current staffing models result in a system where patients are frequently "handed off" at various time intervals to another health care provider. These interruptions in continuity of care can impair the care team's ability to recognize subtle signs of decline that are present in the initial stages of sepsis. Second, while it is easy to recognize someone who needs immediate transfer to the intensive care unit, projecting who will need ICU transfer over the next 24-48 hours given the patient's present trajectory is difficult, even for seasoned clinicians, given the number of parameters (e.g., vital signs, lab results, mental status, etc.) that need to be assessed over time. Third, attempts to determine the severity of illness based upon objective clinical measures fail to account for the patient's baseline and trajectory. For example, most of the models (e.g., MEWS

1

and ViEWS) that have been developed utilize static measures in predictors without taking into consideration the effect of the longitudinal changes in these predictors on outcome such as mortality or ICU admission[5, 6]. These considerations, along with the increasing number of patients that physicians are responsible for, have resulted in intense interest in the development of automated warning systems that can alert the care team to a potential impending deleterious change in clinical status.

With the development of computerized charting and electronic medical records (EMRs), there is now ready access to vital signs and laboratory values over the patient's entire hospital course. The ease with which these predictors can be accessed makes including these longitudinal trends into models of prediction for ICU admission tenable. Indeed, the Centers for Medicare and Medicaid Services have offered financial incentives for the "meaningful" use of EMRs and other health information technology (HIT). Presently, very little work has been done examining how the EMR could be used to make triage decisions in patients.[REF- NEJM editorial Feb 2013 Chen and Hofer] We therefore undertook this study to determine whether longitudinal patterns of routinely recorded clinical parameters, including vital signs and laboratory tests, could be used to identify patients with sepsis who had impending need for ICU transfer. We chose to examine a relatively homogenous cohort of adult patients admitted to a hematologic specialty ward with either underlying hematologic malignancy or who were post hematopoietic stem cell transplant, who subsequently developed sepsis and needed ICU transfer. We predicted that in this group of patients, we could use longitudinal data from the EMR to build a prediction model for ICU transfer with high accuracy.

2

Hypothesis

We hypothesize that we could use routine vital signs and laboratory values that are already being collected in hospitalized patients to develop a model that could predict the development of septic shock before it occurs. We define these routine vital signs and laboratory values as clinical biomarkers. Specifically, this includes diastolic blood pressure, systolic blood pressure, pulse pressure, heart rate, respiratory rate, temperature, sodium, potassium, chloride, total CO2 (bicarbonate), BUN, creatinine, glucose, white blood cell count, hemoglobin and platelet count. In particular, we wanted to focus on these clinical biomarkers as they were readily available for each patient and could be easily incorporated into an early warning system for development of septic shock. While there are other covariates (e.g., diagnoses at admission, reason for admission, treatments received and comorbidities) that are important, these are not readily available for real-time monitoring, hence they were not incorporated into the models. This is not unlike other models that have been proposed for the prediction of ICU admission[3, 5, 7-9]. The static covariates (in addition to the clinical biomarkers) that we included were age and sex which were both readily accessible and able to be monitored in real-time.

Methods

The study was a retrospective study utilizing patient data from January 1, 2010 to December 31, 2010. The study population included hospitalized adult patients at the Ronald Reagan UCLA Medical Center admitted to the leukemia/stem cell transplantation floor. The majority of these patients were diagnosed with leukemia/lymphoma and received chemotherapy, stem cell transplantation (allogeneic and autologous) or were admitted for neutropenic surveillance. The exclusion criteria were age younger than 18 years, if the patients were made DNR/DNI or transitioned to comfort care and shock that

3

was defined as other than septic shock (e.g, hemorrhagic shock or cardiogenic shock). In addition, patients that were not normally admitted to the oncological floor but who were boarded on those floors were excluded. There were 14 of these patients, and they were admitted for diagnoses such as rheumatological diseases, prior renal transplant and 1 patient was admitted for wrist pain. Patients that were initially transferred to the ICU for observation only to develop septic shock more than 1 hour after transfer to the ICU were excluded from the study. The reason these patients were excluded was because the plan was to develop a warning system that depended on the measurements performed on the medical oncological floor rather than the increased number of measurements that are often obtained in the ICU. Patients that were transferred to the ICU for reasons other than septic shock were excluded from the study. These exclusions included transfers for respiratory distress, including patients that were initially intubated and then developed vasopressor requirements only after intubation (excluded because some of the induction agents used for endotracheal intubation can cause hypotension requiring vasopressor use). In addition, congestive heart failure and hemorrhagic shock as the causes of shock would be excluded. The floor patients that remained on the floor until discharge from the hospital were the control patients. The patients that were admitted to the ICU for septic shock, defined as requiring the initiation of vasopressors after transfer to the ICU, were included as the study patients. Typically, the vital signs (blood pressure, heart rate, respiratory rate, temperature) were measured every 4 hours by the staff on the medical floor. The standard labs were measured once a day.

Histograms were generated for each clinical biomarker, and logarithmic transformations were performed if the distribution was not normal. In particular, the distributions of BUN, white blood cell count and platelet count were not normally distributed.

A multivariate mixed effects logistic regression was performed to demonstrate that changes in the clinical biomarkers of each patient could be used to determine development of septic shock. The analysis was clustered on the individual patient. The final model was arrived from the full model by backward stepwise logistic regression, removing the covariate with the highest p value step-by-step until the AIC (Akaike information criterion) was at a minimum. Each clinical biomarker (vital sign and laboratory value) included a covariate that included the initial value upon admission and then a change from the initial value (at every time point where the vital sign or laboratory value was measured). For instance, there was a covariate for the initial diastolic blood pressure upon admission and also a covariate that was the change in value of the diastolic blood pressure as compared to the initial diastolic blood pressure. The change in diastolic blood pressure was calculated for each patient as the change from their initial diastolic blood pressure upon admission. Similarly, other covariates were created for each vital sign and for each laboratory value. The initial value term could only be removed if the change in value of the corresponding term was first removed by backward stepwise regression. The static covariates, namely age and sex, were included in the full model because these covariates are readily accessible and are amenable to real-time monitoring. Other important static covariates (e.g., treatment received, time of antibiotics, diagnosis and other comorbidities) were not included because they are not easily amenable to real-time monitoring in our current system. However, treatment received (chemotherapy causing neutropenia, chemotherapy not causing neutropenia, allogeneic stem cell transplant received and autologous stem cell transplant received) and cancer diagnosis was included in one analysis and both were removed from the final model after backward regression, resulting in our final model. Like other current models of early warning, these static covariates were not included in the other current models of early warning[3, 5, 7-9]. Analysis was performed using the

5

lme4 package in R. Significance was defined at a level of p < 0.05 without correction for multiple comparisons. The ROC curves were developed using the ROCR package in R.

Results

Study population characteristics

Table 1 shows the characteristics of the study population, separated by the control group compared to the group of patients that developed septic shock. In addition, the cancer diagnoses and treatments received are noted. The patients in the septic shock group were admitted primarily with a diagnosis of acute myelogenous leukemia (AML) and were admitted for either chemotherapy that resulted in leukopenia, admitted for neutropenic surveillance or admission for allogeneic stem cell transplantation. The cancer diagnoses and treatments received in the control group were more varied. The median times to either discharge or development of septic shock were similar between the control group and the septic shock group, respectively. Figure 1 illustrates the number of patients that were included in the study and the number of patients that were excluded, along with the reasons for exclusion. There were a total of 12 patients that were initially transferred to the ICU for reasons other than septic shock. These included 6 patients that were initially intubated for respiratory failure and then were placed on vasopressors, 1 that was intubated for respiratory failure but never placed on vasopressors, 1 that was transferred for respiratory distress and atrial fibrillation, 1 that was transferred for hemorrhagic shock, 1 that was transferred after developing a respiratory code on the medical oncological floor, 1 that was transferred for pulmonary embolism requiring vasopressors and 1 that was excluded because the patient was initially transferred to the ICU for observation given respiratory distress and eventually developed septic shock. For the control patients, 11 were excluded because they were DNR/DNI or made comfort care only and 14 were excluded because the patients were

not ones normally admitted to the oncological floor (e.g., admission for rheumatological diseases, prior renal transplant and wrist pain).

Multivariate Logistic Regression Analysis

Table 2 shows the results of the final mixed effects multivariate logistic regression model for vital signs after backward stepwise regression. The equations for the mixed effects multivariate logistic regression model are included in the statistical appendix below. Sex and age were included as static covariates in the initial full model, however sex fell out of the final model. These two static covariates were included because they were available in the real-time monitoring system. As expected, changes from the initial values of several key vital signs are associated with an increased odds ratio of developing septic shock. In particular, a decrease in systolic blood pressure and increase in heart rate from initial values are associated with increased odds ratio of developing septic shock ($p < 0.05$). An increase in temperature from the initial temperature was also associated with development of septic shock ($p < 0.01$). An initial higher heart rate ($p < 0.05$) and initial higher respiratory rate ($p < 0.05$) are also associated with development of septic shock. Finally, an increasing age was found to be associated with development of septic shock ($p < 0.001$).

To evaluate whether other covariates would be more important in predicting septic shock, a separate analysis was performed including a static covariate that represented the type of treatment received (e.g., chemotherapy causing leukopenia, chemotherapy but no associated leukopenia, allogeneic stem cell transplantation and autologous stem cell transplantation), cancer diagnosis, age and sex. As before, the final model after stepwise backward regression kept only age as the static covariate, removing sex, the type of treatment received and cancer diagnosis from the final model. Therefore,

including type of treatment received and cancer diagnosis in the full model (along with age, sex and longitudinal vital covariate) resulted in the same final model as one that only included age and sex, after stepwise backward regression. Figure 2 shows the ROC curve for this final model utilizing only the vital signs with an AUC (area under the curve) of 0.985. If we use as the last measurement, the vital sign measurement 2 hours before the development of septic shock, the performance of the model is slightly worse but the ROC curve still has an AUC of 0.980 (figure 3). Moving 4 hours back from the time of development of septic shock, the performance of the model is diminished but still acceptable with an AUC of 0.967 (figure 4).

Table 3 shows the results of the final mixed effects multivariate logistic regression model for laboratory values after backward stepwise regression. Significant covariates included increases in sodium, decreases in chloride, decreases in total CO_2 and decreases in hemoglobin. While not statistically significant, increases in white blood cell count and decreases in platelet count are associated with development of septic shock.

Discussion

The use of readily measured clinical biomarkers (routine vital signs and laboratory studies) can be used to predict the development of septic shock for patients on the medical oncological floors where patients are primarily admitted for chemotherapy, neutropenic surveillance or stem cell transplantation. In the multivariate logistic regression model using vital signs, a decrease in systolic blood pressure, an increase in heart rate and an increase in temperature were associated with the development of septic shock (table 2). This is consistent with the pathophysiology of septic shock where peripheral vasodilation results in a drop in blood pressure. The increase in heart rate represents a response to the decrease in blood pressure. In addition, the increase in

8

temperature was also expected as the physiological response to infection is an increased temperature. The diastolic blood pressure covariates fell out of the final model as they measured approximately the same thing as the systolic blood pressure. Increased age was noted to be predictive of development of septic shock, like prior studies.[10] Moving backwards in time from the time of septic shock diminished the performance of the model, however it continued to perform at an acceptable level (figures 2-4).

While the mixed-effects multivariate logistic model using laboratory data only was not as accurate as the model utilizing vital signs, it did suggest some intriguing associations (table 3). In particular, a decrease in total CO_2 was associated with development of septic shock. This makes physiological sense in that the increase in lactic acidosis with septic shock is buffered by the bicarbonate in the patient, lowering the total CO_2. The increase in sodium may be due to increasing use of intravenous fluids prior to development of septic shock. Therefore the increasing sodium may reflect physician intuition about impending septic shock, as they perform maneuvers on the medical floor to augment a slight decrease in blood pressure by administering more intravenous fluids in the form of normal saline. There is also suggestion that increased sodium is associated with increased mortality in the ICU[11].

In addition, a decrease in hemoglobin is associated with development of septic shock (table 3). This is consistent with the pathophysiology of septic shock where inflammation causes a decrease in production of red blood cells causing hypo-proliferative anemia and disseminated intravascular coagulation causes hemolytic anemia[12]. Another potential cause of the anemia may be dilutional as the patients may be receiving intravenous fluid (normal saline) that would dilute the blood. Similar to the anemia

associated with septic shock, thrombocytopenia (though not statistically significant in this analysis) can be the result of inflammation causing hypo-proliferative thrombocytopenia and disseminated intravascular coagulation causing consumptive thrombocytopenia. While not statistically significant, an increase in age was associated with development of septic shock (p = 0.1555) which is consistent with other findings. Figure 5 shows the ROC curve for this final model utilizing only the laboratory values with an AUC of 0.761. Unlike the mixed effects multivariate logistic regression model using vital signs, the one utilizing only laboratory values does not perform as well.

As noted in the introduction, our focus on the readily available vital signs and routine laboratory studies as covariates was partially because the real-time monitoring system that is currently implemented does not incorporate other important covariates (e.g., diagnoses at admission, reason for admission, treatments received and comorbidities) that may have important effects on the outcome. However, as discussed above, the treatments received (e.g., chemotherapy or stem cell transplantation) and cancer diagnosis did not make it into the final model for the mixed effects multivariate logistic regression model.

Previous studies have used clinical biomarkers (e.g., MEWS, ViEWS and use of recursive partitioning techniques) to predict the development of sepsis, however they have relied on fixed categories for vital signs and laboratory values[3, 5, 7-9]. As is demonstrated in this study, there is utility in knowing the changes in longitudinal clinical biomarkers. For instance, while a heart rate of 80 bpm may still be in the normal range and considered normal in models that use fixed categories, if one were to be given information that the patient's heart rate upon admission was 50 bpm, it would be seen as an increase in 30 bpm from the initial heart rate, raising some concern that there may be

a change in the clinical picture. Because these other models used fixed categories across different patients, these methods do not take advantage of the information in the changes in these clinical biomarkers over the course of the hospitalization of a patient.

In addition, the recursive partitioning technique used in other studies[9] did not take into consideration the multiple repeated measures on each individual patient, as the analysis was not clustered on the individual patient. In the mixed effects multivariate logistic regression used here, the analysis was clustered on each patient and the changes in these clinical biomarkers are tracked by a change in these values from their initial value upon admission.

One limitation with the current mixed effects logistic regression model used here is that it does not incorporate other clinical factors (e.g., treatment received, whether antibiotics were given, diagnosis, and comorbidities) that would have a direct impact on clinical outcome, however other current models do not incorporate these static covariates[3, 5, 7-9]. An attempt to include sex, treatment received and cancer diagnosis resulted in the same final model as one that only included age as the only static covariate. These static covariates (other than age and sex) were not included because they were not readily accessible in the current electronic medical record system and also because we wanted to develop a model that relied primarily on vitals signs and laboratory studies. As more of these clinical factors become digitized and accessible to real-time monitoring, they will be incorporated into future renditions of the model. Another limitation is that we did not evaluate interaction terms due to our limited cases of septic shock. This is another venue that is worth pursuing as it is readily plausible that a patient with decreasing systolic blood pressure and increasing heart rate may have an interaction that increases the odds ratio of developing septic shock above just that of decreasing systolic blood

11

pressure or increasing heart rate alone. However, despite the current limitations of our study, we demonstrated good performance even 2 to 4 hours from the last vital sign measurement, suggesting that this approach may be valid and could be used to serve as an early warning for development of septic shock (figures 3 and 4).

Another limitation of the current model is that it can not predict a time to event, in this case, the development of septic shock. An attempt had been made to use joint modeling as a method to model prediction of time to development of septic shock[13]. However, because of the difficulty in simultaneously modeling multiple time-varying covariates and inability to accurately the non-linear time trends in these clinical biomarkers, this method of analysis was abandoned in favor of the mixed effects multivariate logistic regression model as this analysis could take advantage of the information in multiple clinical biomarkers.

Another limitation is the small sample size. This small sample size limited our ability to include interaction terms in the mixed effects multivariate logistic regression model. More importantly, the small sample size prevents us from obtaining accurate statistical estimates. Typically, we would want 10-15 cases for each term in logistic regression to obtain valid statistical estimates, however we were limited in the lack of cases in 2010. An ongoing effort is being made to obtain more cases in order to improve the statistical estimates and then to validate the model.

Intriguingly, consistent with the expected pathophysiology of septic shock where peripheral vasodilation with preserved to higher-than-normal stroke volumes occur, the pulse pressure increases (reflecting an intact stroke volume) while the diastolic blood pressure decreases (reflecting peripheral vasodilation) in the patients that developed

septic shock compared to the control group of patients (table 2). This is similarly demonstrated by the increase in pulse pressure/diastolic blood pressure ratio in patients that developed septic shock compared to the control patients. While we did not study patients that developed cardiogenic shock, we would expect that the pulse pressure would be decreased in these patients due to a decrease in stroke volume secondary to the pathophysiology of cardiogenic shock. In addition, we would expect that there would be compensatory peripheral vasoconstriction resulting in a smaller decrease in diastolic blood pressure. Thus, in contrast to septic shock, we might see a decrease in the pulse pressure and pulse pressure/diastolic blood pressure ratio in cardiogenic shock compared to septic shock. In future studies, we propose studying whether changes in pulse pressure and pulse pressure/diastolic blood pressure ratio (or pulse pressure/systolic blood pressure ratio) may be used to distinguish between septic shock and cardiogenic shock earlier, leading to distinguishing these patients appropriately and treating them in a more timely fashion.

Future directions will involve validation of the findings of the mixed effects multivariate logistic regression model on a different cohort after collection of more cases to complete development of the model, including analysis of interaction terms. We expect the AUC of the validation cohort to be lower than that shown in our study. If the results are promising, then we plan to implement a real-time monitoring system in the hospital to screen for development of septic shock. This system would then warn the treating floor physicians, alerting them to potential development of septic shock before it occurs, allowing for appropriate changes in medical therapy if needed, e.g., initiation or change of antibiotics and a search for source of infection. However, it might also facilitate a quicker transfer to the ICU if needed, as there are studies that show benefit to earlier transfer compared to emergent transfers to the ICU where the patient has already

13

deteriorated[14, 15]. By alerting the treating floor physician that there may be a development of septic shock with extremely poor prognosis, earlier discussions of goals of care may be initiated so that patients and their families may be better prepared. In addition, as more clinically relevant static covariates are able to be electronically accessed, we will incorporate these covariates into the model to see if the performance improves. Finally, models of prediction of respiratory failure and ARDS (acute respiratory distress syndrome) for patients on the medical/surgical floors will also be pursued, along with models for predicting other emergent ICU transfers such as cardiogenic shock.

Statistical Appendix

Joint modeling[13] was initially chosen to model prediction of time to septic shock, as clinical biomarkers are endogenous covariates. It also has the advantages of removing measurement errors and short term biological fluctuations from the observed data. The details of the joint model are listed in the paragraph below. The results of the joint modeling analysis are listed in table 4. In contrast, using a time-dependent Cox proportional hazards model for predicting time to septic shock would be inappropriate given that it would treat the clinical biomarkers as exogenous covariates rather than as endogenous covariates. However, that being said, it would be an analysis to attempt given that it does not assume a form for the time trend of the clinical biomarkers, and we plan on pursuing this analysis as another direction. Joint modeling has previously been used in cancer and AIDS literature[16]. In general, most literature has used univariate time-to-event data with very few studies using multivariate time-to-event data[17]. The use of a univariate longitudinal joint model was attempted in this study. Limitations in this approach included the inability to utilize multivariate longitudinal time trends to better develop a prediction model for septic shock. In addition, the restriction that the longitudinal time trends had to be modeled using a linear approach caused the joint

model predictions to be inaccurate. This is, in part, due to the fact that patients are sometimes hospitalized for a while before developing septic shock and the changes in the longitudinal time trends are usually most dramatic around the time of development of septic shock. An example of this is seen in figure 6 where the diastolic blood pressure remains stable throughout the hospitalization but drops near the time of development of septic shock. Thus, using a linear model starting from time of admission, in effect, decreases the impact of the more drastic changes in vitals signs and lab values seen around the time when septic shock develops. Despite all these limitations, table 4 demonstrates that decreases in diastolic blood pressure, decreases in systolic blood pressure and increases in heart rate were associated with the development of septic shock, utilizing the joint modeling approach. However, because of the inaccuracy due to the limitation of the joint modeling approach, we pursued a mixed effects multivariate logistic regression approach which sacrifices time-to-event analysis but allows the integration of multiple covariates simultaneously.

The hazard function for joint modeling is listed below where $M_i(t)$ represents the longitudinal process up to time t for subject i, w_i is the vector of baseline covariates such as age and sex, $h_0(t)$ is the baseline hazard function, g is the vector of regression coefficients for the baseline covariates, $m_i(t)$ represents the time-varying covariate (e.g., diastolic blood pressure).

$h_i(t \mid M_i(t), w_i) = h_0(t)exp(gw_i + am_i(t))$

Exp(a) then represents the relative increase in the risk for an event at time t that results from a one unit increase in the time-varying covariate $m_i(t)$ at the same time point. Exp(g) represents the ratio of the hazards for a one unit change in w_i.

The time-varying covariate is modeled by a linear mixed effects model with a random slope and intercept. The longitudinal sub-model of the joint model is listed below, where $Y_i(t)$ is the vital sign data, $m_i(t)$ is the underlying trajectory of the time-varying covariate, $e_i(t)$ is the error term, b_0 represents the intercept for the fixed effects and b_1 represents the slope for the fixed effects. In addition, b_{0i} and b_{1i} represents bivariate normal variables to represent the random intercept and random slope, respectively.

$Y_i(t) = m_i(t) + e_i(t)$

$m_i(t) = b_0 + b_1 t + b_{0i} + b_{1i} t$

While the trend in vitals signs and laboratory values are not necessarily linear, a linear mixed effects model was used as a first approximation because the software package responsible for joint modeling could not handle nonlinear time trends in the longitudinal trend component. Again, figure 2 serves as an example. Because the actual longitudinal trends were not linear and the joint modeling software assumes a linear longitudinal trend in the clinical biomarkers, the prediction of development of septic shock was not accurate. In addition, an attempt was made to fit splines to the longitudinal trends, however given that the time to development of septic shock was variable depending on the patient, there was not a common knot that could be placed, so the use of splines was unsuccessful.

Given the limitations of the joint modeling approach (inability to use more than one longitudinal covariate and inability to accurately predict development of septic shock), we pursued a mixed effects multivariate logistic regression approach. For the mixed effects multivariate logistic regression model using only vital signs, the AUC was good at 0.985 (figure 2), however we expect that the actual performance on a testing cohort will be

lower. Even going back 2 hours or 4 hours prior to development of septic shock, the performance of the model performed well (figures 3 and 4). One limitation with logistic regression is the inability to determine a time to event. However given that the joint modeling approach produced an inaccurate prediction of septic shock, using the multivariate logistic regression approach gave us the advantage of utilizing multiple longitudinal covariates (changes of vitals signs and laboratory values from their corresponding initial values) and controlling for the other covariates. We did not evaluate for interaction terms as we did not have a large number of cases of septic shock and realize that this is a limitation which will be addressed as we obtain a larger training cohort with more cases of septic shock. From a physiological perspective, there is at least some motivation to look at the interaction between blood pressure and heart rate. A decrease in systolic blood pressure along with an increase in heart rate may represent an interaction that increases the odds ratio of developing septic shock more than that of a decreased systolic blood pressure and an increased heart rate by themselves. In addition, as the real-time monitoring capabilities increase, we plan on incorporating other potentially important covariates (e.g., diagnoses at admission, reason for admission, treatments received and comorbidities), though cancer diagnosis and treatment received did fall out of the final model.

The mixed effects logistic regression model is as follows:

Logit $P(y_{ij} = 1 \mid X_{ij}) = bX_{ij} + e_i$ where y_{ij} is the outcome measurement on subject i at time j, b is a vector of regression coefficients, X_{ij} is a vector of predictors for subject i at time j, e_i is a zero-mean normal variable representing the random intercept. For each subject that enters that ICU for septic shock, y_{ij} is zero except for the last observation and which

17

point y_{ij} = 1. For control subjects that do not enter the ICU and are discharged home, y_{ij} = 0 for all time points j.

In R code, the equation for the full mixed effects logistic regression model using vital signs is listed below.

Septic shock ~ Initial diastolic blood pressure value + Change in diastolic blood pressure value from initial measurement + Initial systolic blood pressure value + Change in systolic blood pressure value from initial measurement + Initial heart value + Change in heart rate value from initial measurement + Initial respiratory rate value + Change in respiratory rate value from initial measurement + Initial temperature value + Change in temperature value from initial measurement + Age + Sex + Random intercept term for each patient

In R code, the equation for the final model using vital signs after backward stepwise regression is listed below.

Septic shock ~ Initial systolic blood pressure value + Change in systolic blood pressure value from initial measurement + Initial heart value + Change in heart rate value from initial measurement + Initial respiratory rate value + Initial temperature value + Change in temperature value from initial measurement + Age + Random intercept term for each patient

In addition, there may be binary covariates that are important in the prediction of septic shock that do not involve actual values. For instance, the very act of ordering a lactate or arterial blood gas may predict the development of septic shock. These binary covariates may not be in and of themselves important pathophysiologically but rather they may

18

serve as a surrogate that the physician on the medical floor is concerned with the patient. In this case, the actual value may be of little value, and the binary act of ordering the test may be of interest. This, too, can be transformed into a rate. For instance, if one were to monitor the number of times these tests were ordered over a rolling time period (for example, 12 hours), it could serve as a rate, and therefore an increasing rate of ordering these tests may serve to "predict" the development of septic shock. In actuality, what this might represent would be that the physician is increasingly concerned about the patient and ordering, in increasing frequency, tests that are not routinely ordered for patients on the medical floor. Therefore, in this case, it may be that instead of ordering more tests in hopes of assuring themselves that the patient is doing well, the mere act of ordering these tests represents an intuition the physician has about impending septic shock, and this intuition is one that the physician should listen to.

Another modeling approach that we plan on pursuing is the use of a rolling time frame and the calculation of a slope for each clinical biomarker. For instance, looking at heart rate, we would compute slopes of the heart rate over a rolling period of 12 hours, for example, where linear regression would be used during this 12 hour window to model the slope of heart rate change. While the overall slope of the course of a biomarker may not be linear, a smaller rolling window over time may be better approximated as linear. This heart rate slope change over time would then serve as a covariate that would vary over time. Similarly, a rolling slope calculation would be performed for each clinical biomarker. Again, given sufficient cases of septic shock, we would include these slope covariates along with their interactions.

Histograms were plotted demonstrating that the vitals signs and laboratory values had a normal distribution. If they did not, then a logarithmic transformation was performed so

that the resulting histogram of the non-Gaussian vital signs and laboratory values had a

normal distribution. In particular, the vital signs (blood pressure, heart rate, respiratory

rate and temperature) had a normal distribution, so no transformation was necessary

(figures 7, 8). The chemistry values were also normally distributed with the exception of

BUN (figure 9, 10). Taking logarithmic transformation of BUN made the distribution

normal, however this did not change the results of the analysis. Hemoglobin had a

normal distribution and no transformation was performed (figure 11). Both white blood

cell count and platelet count had a right skewed distribution and a logarithmic

transformation was able to make the distributions more normal (figure 12). However, the

logarithmic transformation did not significantly change the results. The results of the

mixed effects multivariate logistic regression using laboratory values with the appropriate

logarithmic transformations for initial white blood cell count and initial platelet count are

show in table 5. For comparison, table 3 demonstrates the results without the logarithmic

transformations and that they were not significantly different.

Histograms of the initial values of diastolic blood pressure, systolic blood pressure and

pulse pressure were approximately normal (figure 13). Histograms of the initial values of

the heart rate, respiratory rate and temperature were also noted to be approximately

normal (figure 14). The histograms of the initial values of the sodium, potassium,

chloride and total CO2 were also normal (figure 15). The histograms of the initial values

of the creatinine and glucose were approximately normal and did not change much with

logarithmic transformation (figure 16). The histogram of the initial BUN values was

approximately normal but looked more normal after logarithmic transformation (figure

16). The histogram of the initial hemoglobin values was normal (figure 17). The

histograms of the initial white blood count values and initial platelet values were not

normal, and were normal after logarithmic transformation (figure 18). This is similar to

the discussion above when the values of all the vitals signs and laboratory values were used, instead of just the very first initial values used for the histograms generated in this paragraph.

Figure 1:
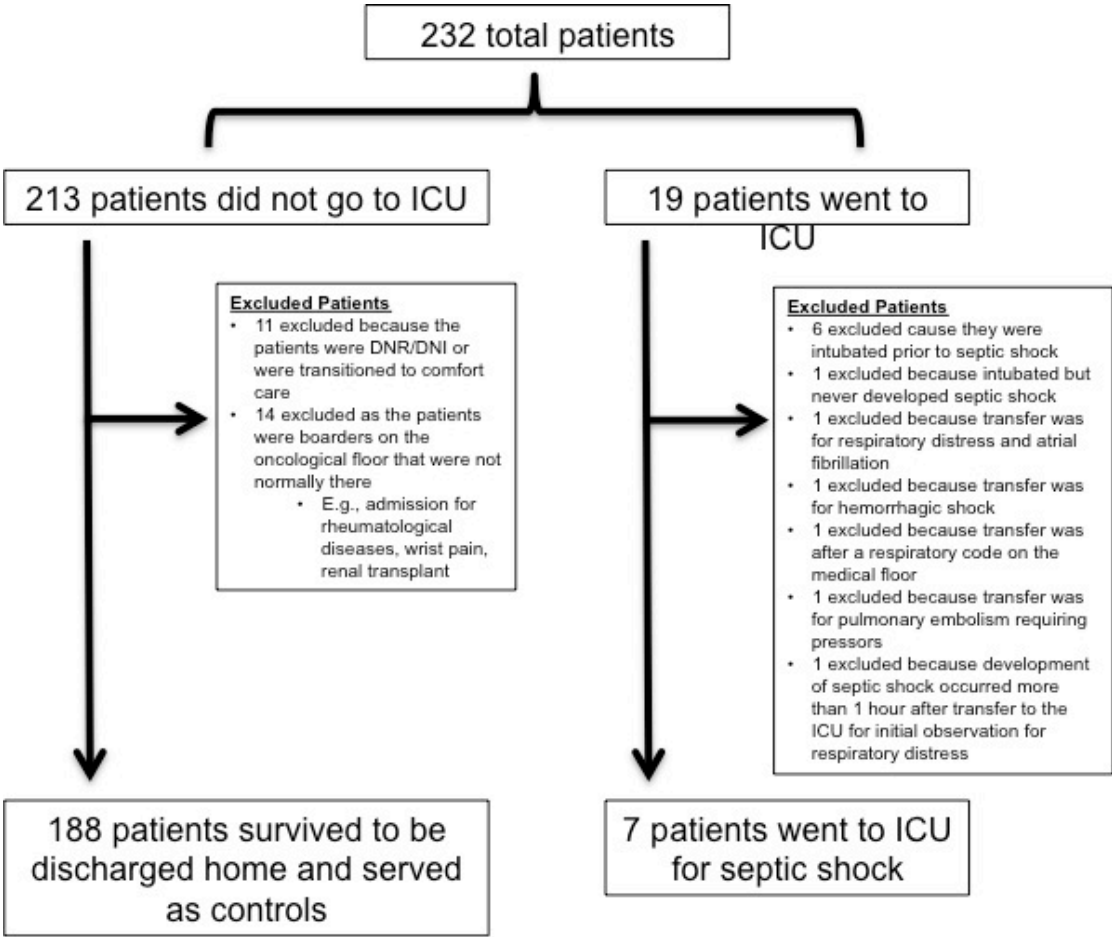**Flowchart of patients that were included and excluded from the study**

232 total patients

213 patients did not go to ICU

19 patients went to ICU

Excluded Patients
- 11 excluded because the patients were DNR/DNI or were transitioned to comfort care
- 14 excluded as the patients were boarders on the oncological floor that were not normally there
  - E.g., admission for rheumatological diseases, wrist pain, renal transplant

Excluded Patients
- 6 excluded cause they were intubated prior to septic shock
- 1 excluded because intubated but never developed septic shock
- 1 excluded because transfer was for respiratory distress and atrial fibrillation
- 1 excluded because transfer was for hemorrhagic shock
- 1 excluded because transfer was after a respiratory code on the medical floor
- 1 excluded because transfer was for pulmonary embolism requiring pressors
- 1 excluded because development of septic shock occurred more than 1 hour after transfer to the ICU for initial observation for respiratory distress

188 patients survived to be discharged home and served as controls

7 patients went to ICU for septic shock

Figure 2:
ROC curve for the mixed effects multivariate logistic regression model for vital signs only. The AUC is 0.985.

ROC Curve for Logistic Regression Model Using Vitals Only

AUC = 0.985

True positive rate
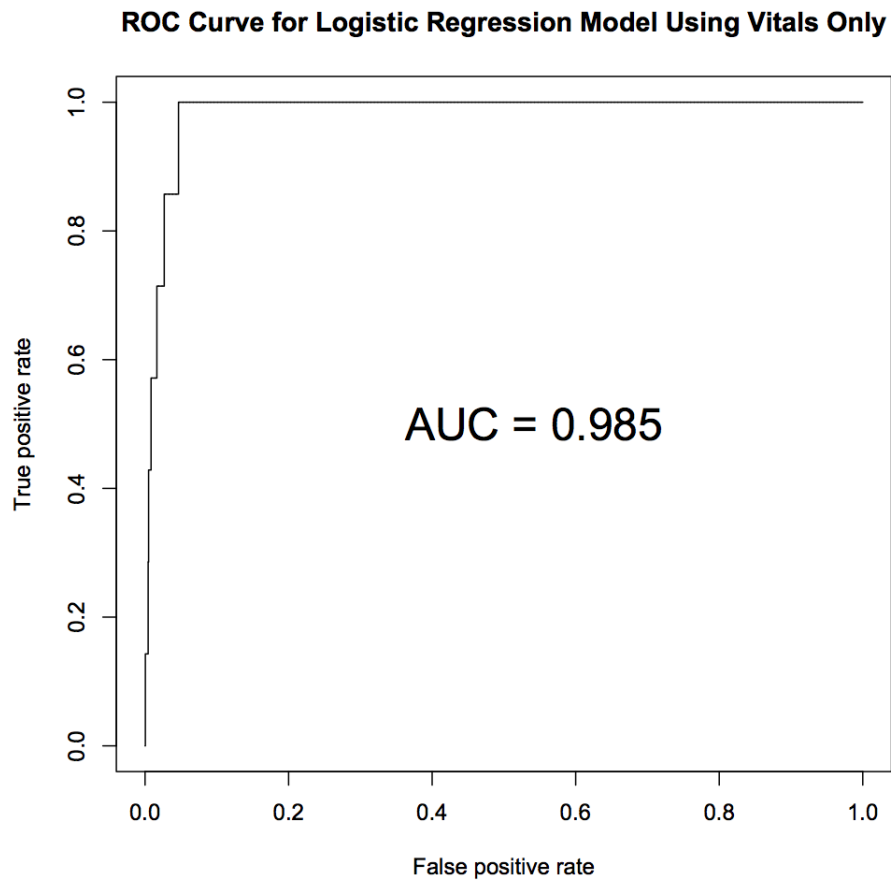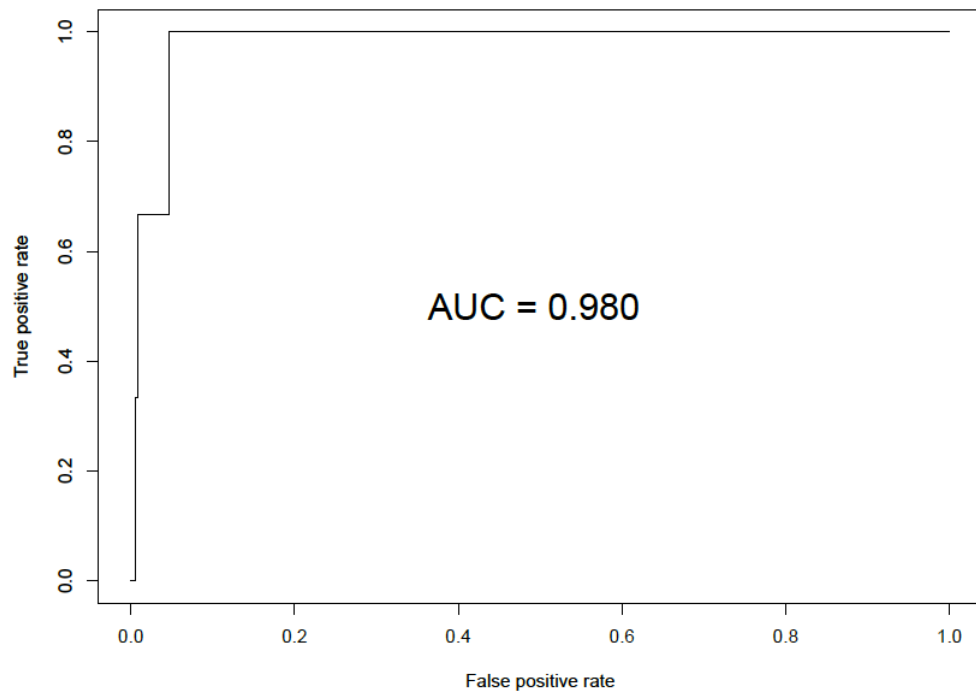
False positive rate

Figure 3:
ROC curve using vitals only, however in this case the last measurement was taken 2 hours before development of septic shock. The performance is slightly worse with an AUC of 0.980 as compared to figure 2.

ROC Curve for Logistic Regression Model Using Vitals Only, 2 Hours Before Septic Shock

AUC = 0.980

Figure 4:
ROC curve using vitals only, however in this case the last measurement was taken 4 hours before development of septic shock. The performance is slightly worse with an AUC of 0.967 as compared to when the last measurement was taken 2 hours before development of septic shock.

ROC Curve for Logistic Regression Model Using Vitals Only, 4 Hours Before Septic Shock

AUC = 0.967
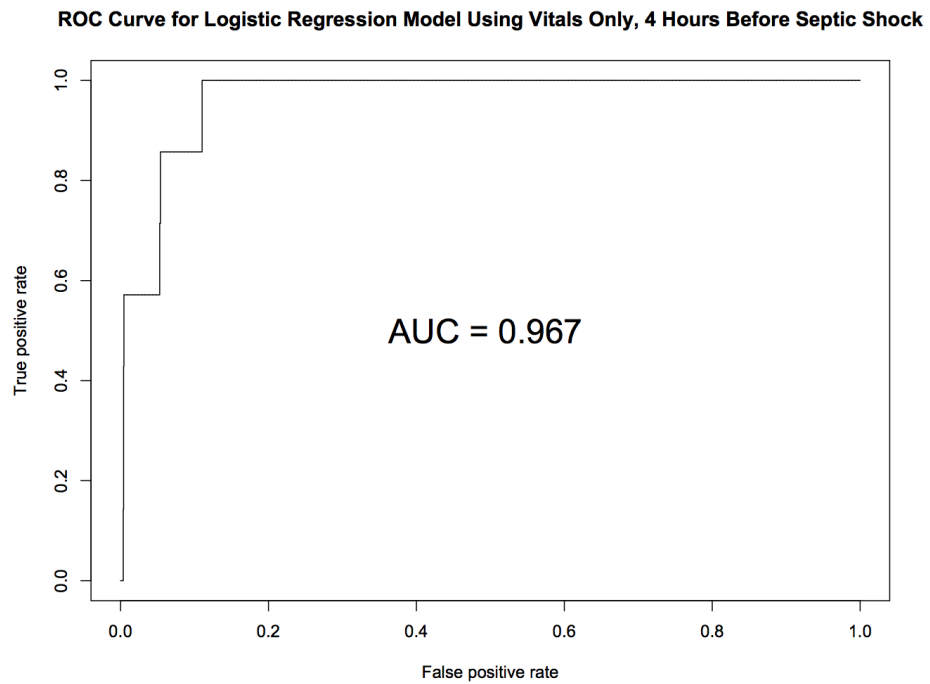
Figure 5:
ROC curve for the mixed effects multivariate logistic regression model for laboratory values only

ROC Curve for Logistic Regression Model Using Lab Studies Only

AUC = 0.761
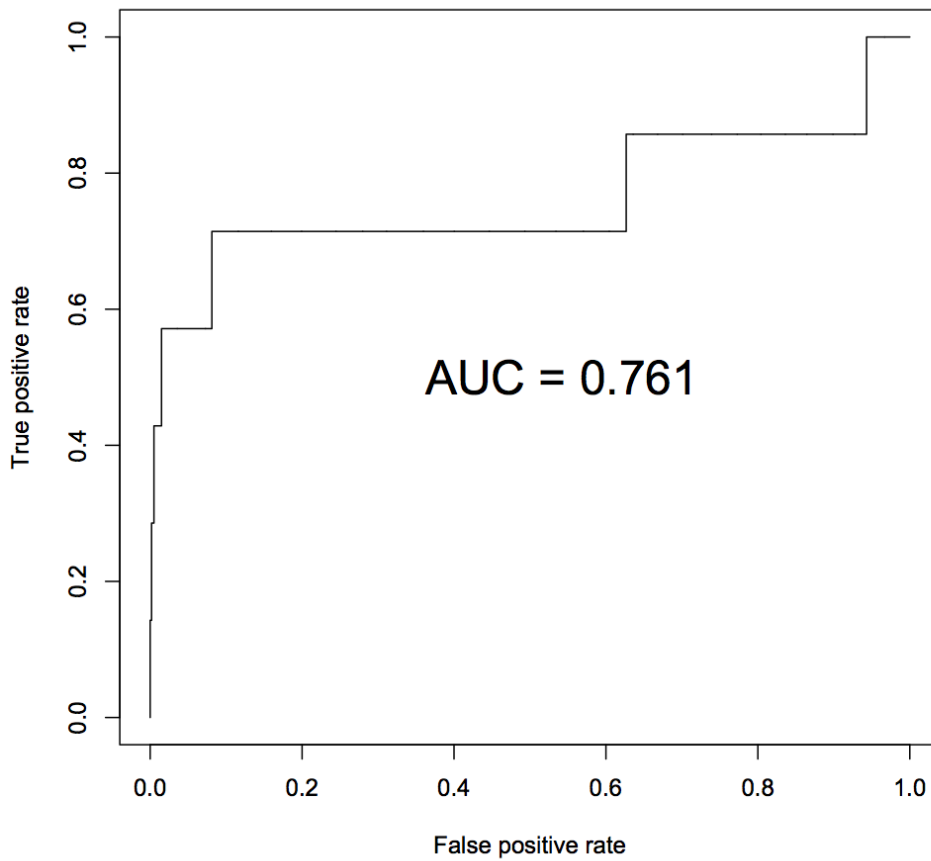
Figure 6:
Time trend for diastolic blood pressure for representative patient that developed septic shock. The last time point represents the measurement prior to admission to the ICU for septic shock. The black line represents the linear fit through the data. Notice, however, that most of the changes occurs close to the time of septic shock and that the linear fit is a poor fit. The decrease in diastolic blood pressure is consistent with the peripheral vasodilation associated with septic shock.
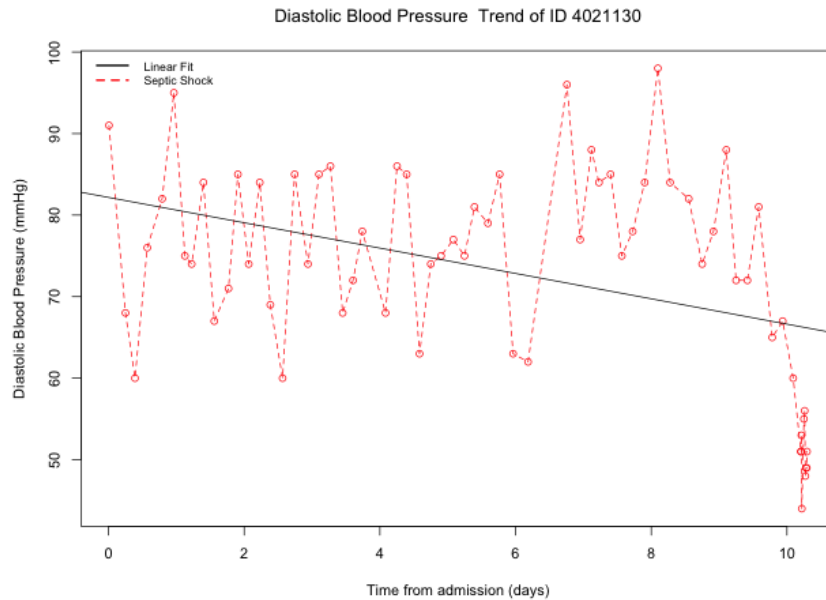
Figure 7:
Histogram of blood pressure associated vitals signs showing that the distributions are approximately normal.
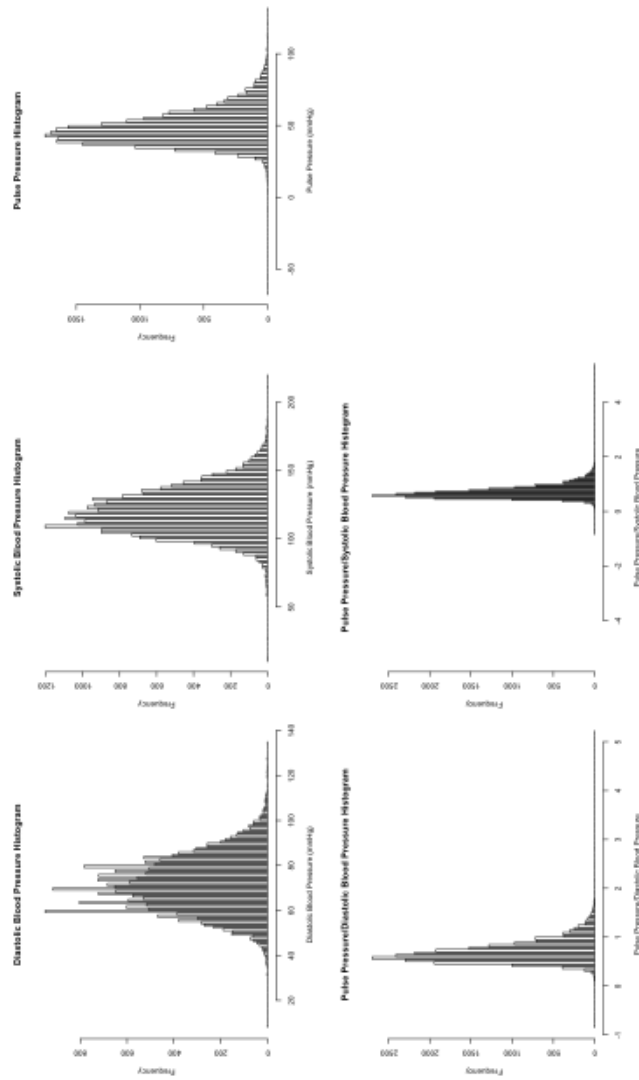
Figure 8:
Histograms of heart rate, respiratory rate and temperature showing that the distributions are approximately normal.
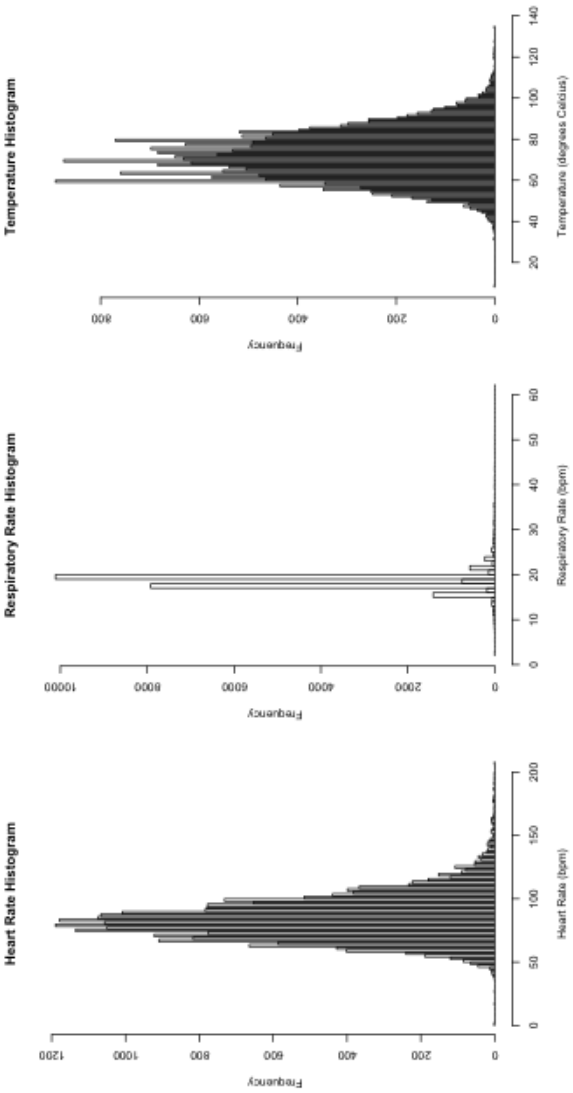
Figure 9:
Histograms of sodium, potassium, chloride and total CO2 (bicarbonate) showing that they are approximately normal.
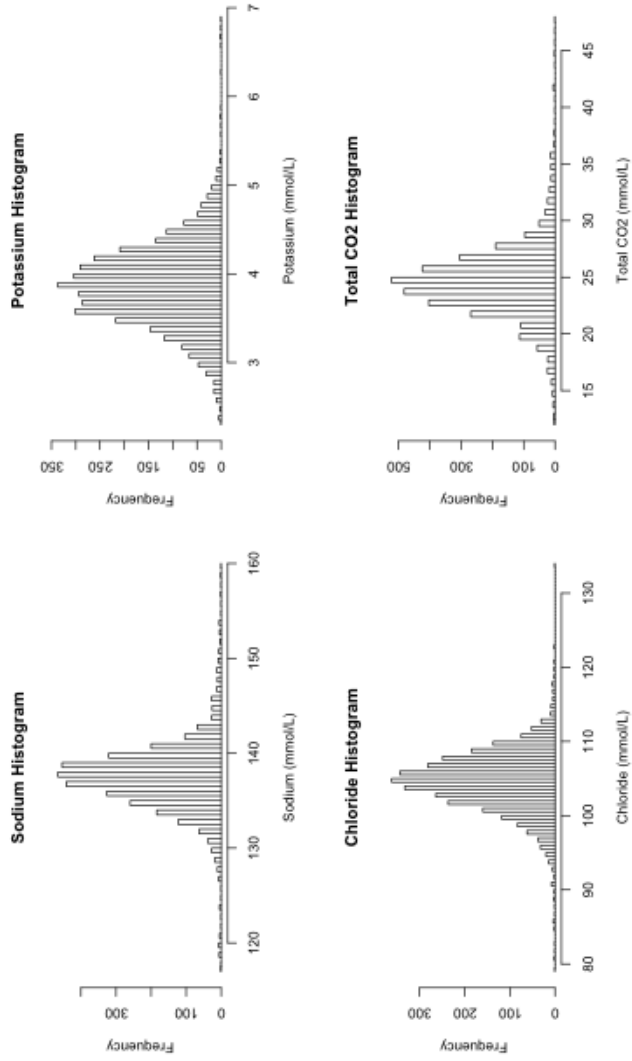
Figure 10:
Histograms of BUN, creatinine and glucose along with histograms of their logarithmic transformations. Logarithmic transformation of BUN was eventually performed because this transformation produced a more normal distribution. Logarithmic transformations were not performed for creatinine or glucose because the logarithmic transformations did not change the distribution significantly from the non-transformed histograms.
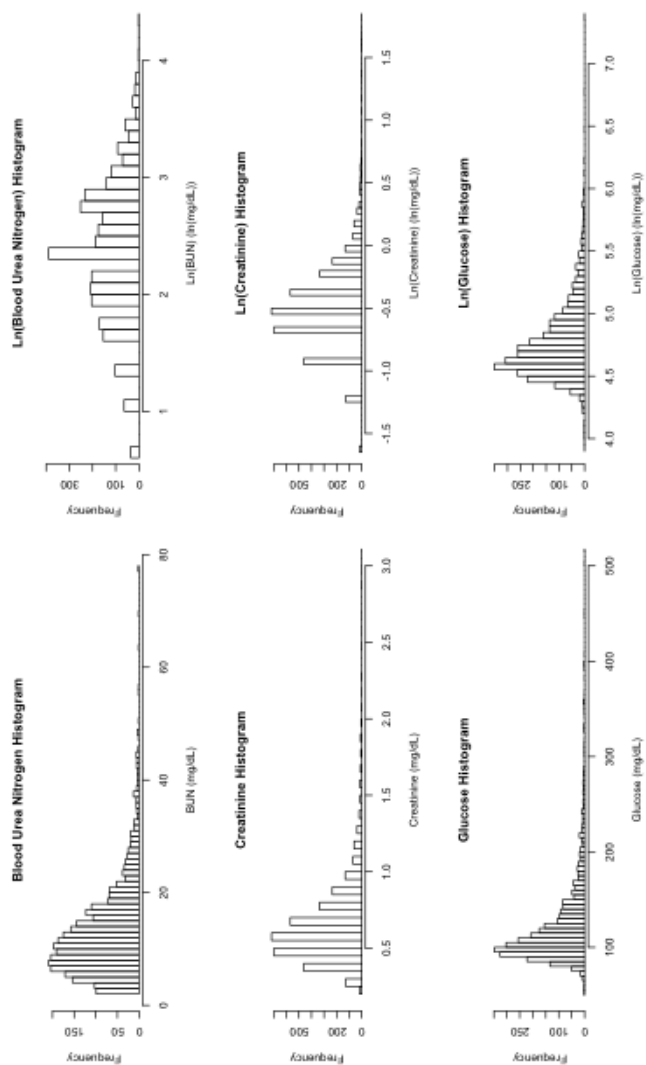
Figure 11:
Histogram of hemoglobin showing that the distribution is approximately normal.
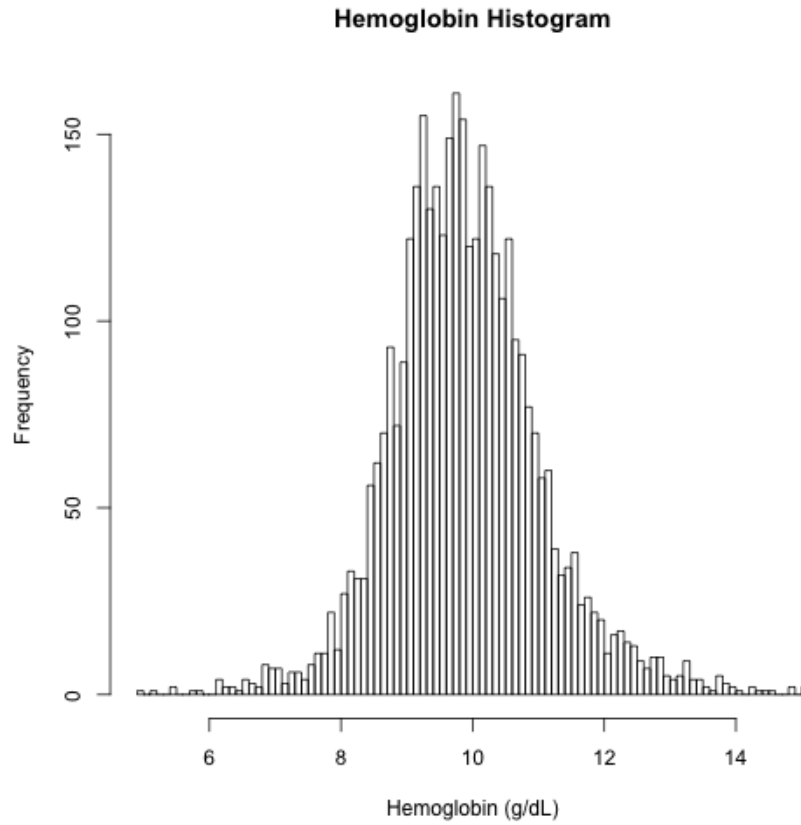

Hemoglobin Histogram

Figure 12:
Histograms of the white blood cell count and platelet count and also of their logarithmic transformations showing that the logarithmic transformations produced a more normal distribution. Logarithmic transformations were performed for WBC and platelet count, as the logarithmic transformation made the distributions more normal.
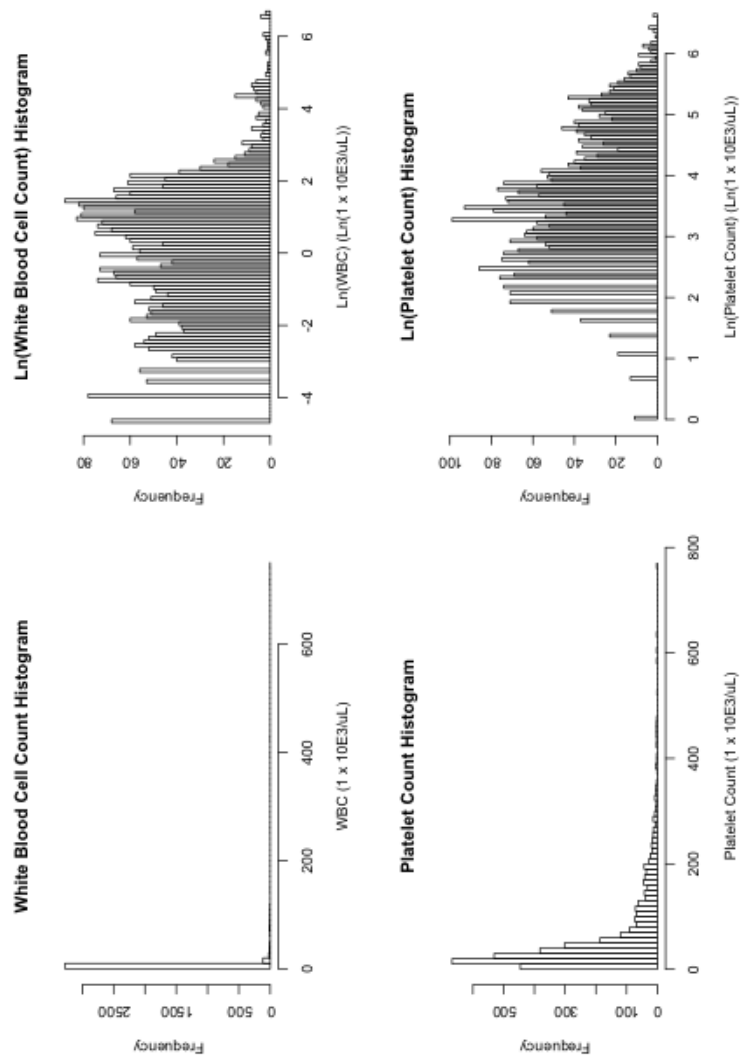
Figure 13:
Histograms of the initial measurements of diastolic blood pressure, systolic blood pressure and pulse pressure. The distributions are approximately normal.
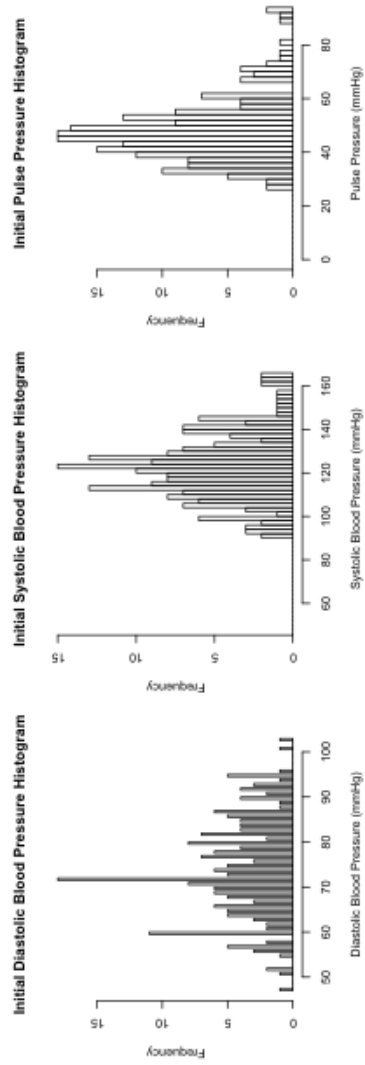
Figure 14:
Histograms of the initial measurements of the heart rate, respiratory rate and temperature. The distributions are approximately normal.
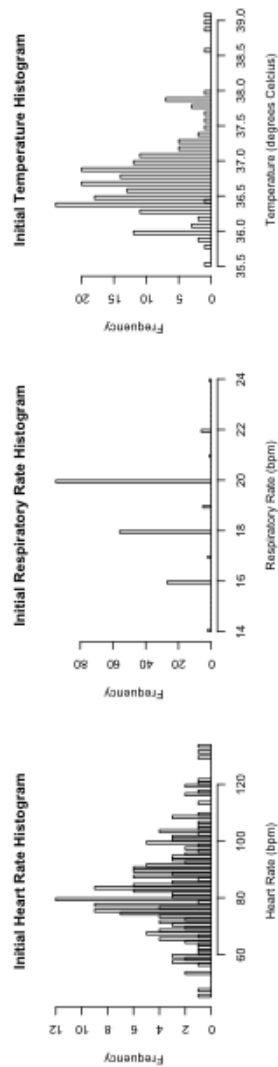
Figure 15:
Histograms of the initial values of sodium, potassium, chloride and total CO2 (bicarbonate) showing that they are approximately normal.
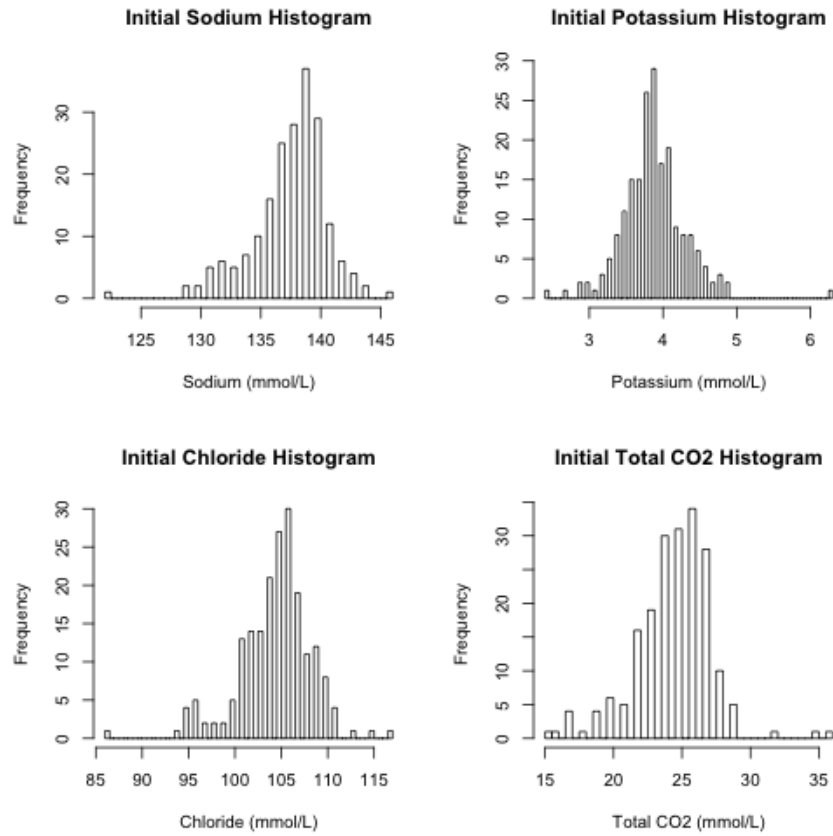
Figure 16:
Histograms of the initial values of BUN, creatinine and glucose along with histograms of their logarithmic transformations. Logarithmic transformation of BUN was eventually performed because this transformation produced a more normal distribution. Logarithmic transformations were not performed for creatinine or glucose because the logarithmic transformations did not change the distribution significantly from the non-transformed histograms.
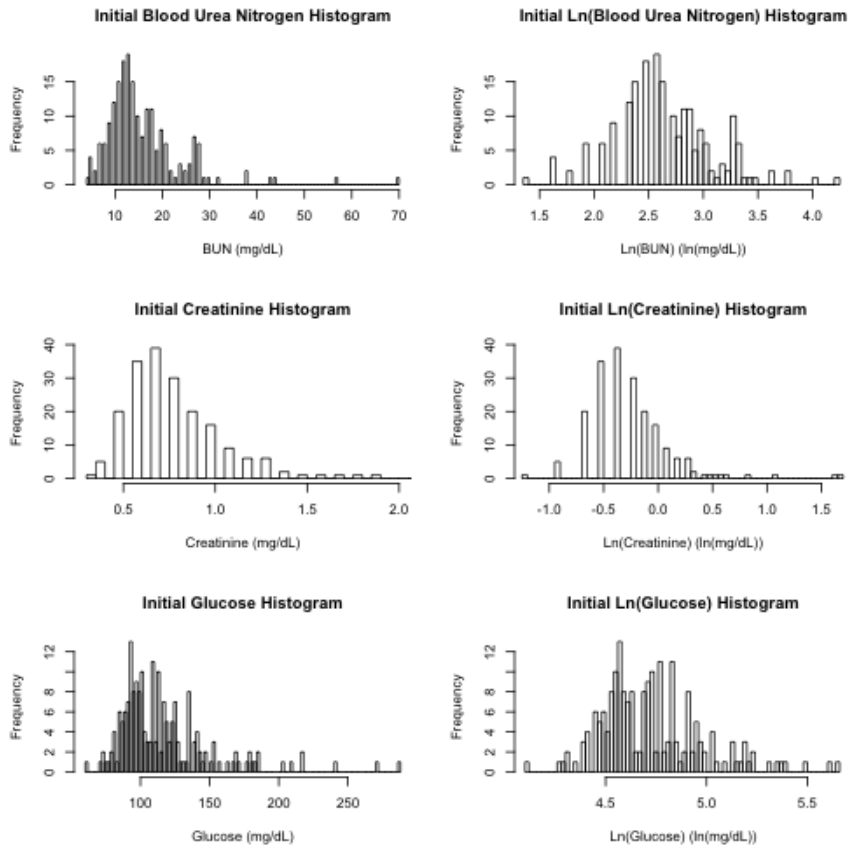
Figure 17:
Histogram of the initial values of hemoglobin showing that the distribution is approximately normal.

Initial Hemoglobin Histogram
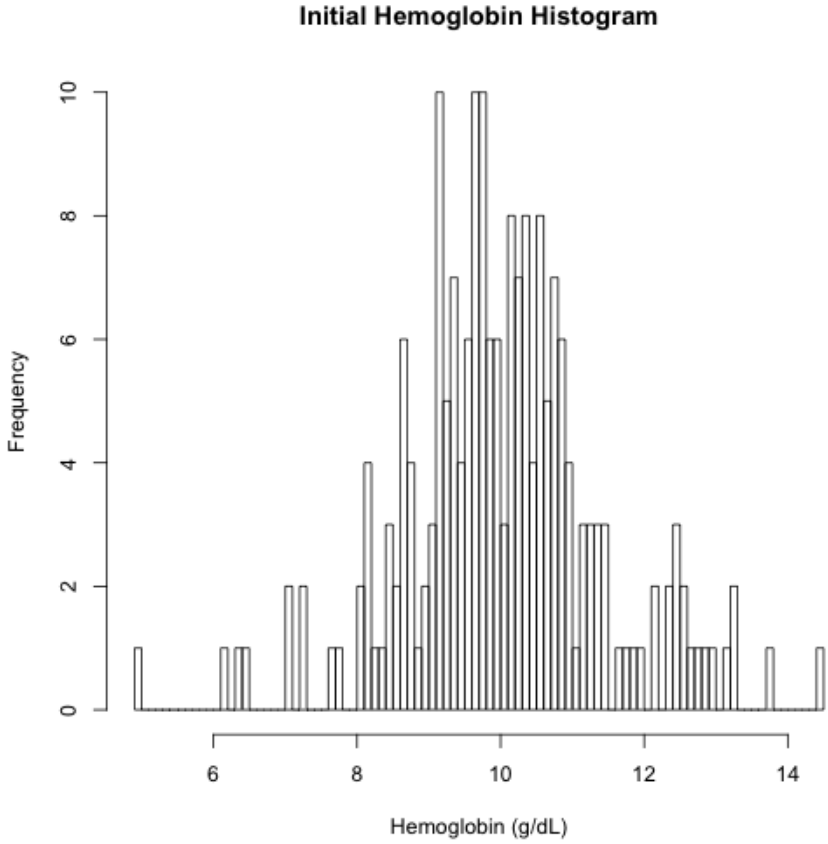
Figure 18:
Histograms of the initial values of white blood cell count and platelet count and also of their logarithmic transformations showing that the logarithmic transformations produced a more normal distribution. Logarithmic transformations were performed for WBC and platelet count, as the logarithmic transformation made the distributions more normal.

Table 1: Demographics

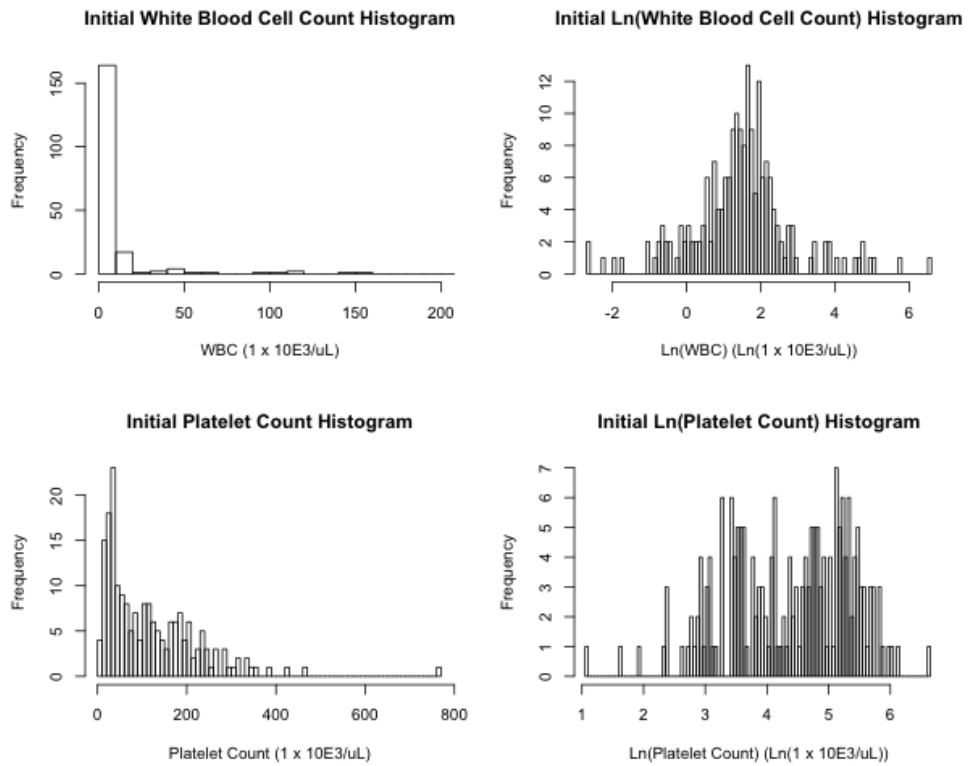| Characteristic	Control Group (n = 188)	Septic Shock Group (n = 7)
Male sex (%)	56.91489362	57.14285714
Mean age (years)	49.17	60.43
Median time to discharge home or development of septic shock	16.11 days	17.53 days

Cancer Diagnosis

	Control Group (n = 188)	Septic Shock Group (n = 7)
AML	58 (30.85%)	5 (71.43%)
ALL	24 (12.77%)	1 (14.29%)
CLL	6 (3.19%)	1 (14.29%)
Chronic myeloid leukemia	4 (2.13%)	0
Lymphoma	44 (23.40%)	0
Multiple myeloma/Plasma cell dyscrasia	12 (6.38%)	0
Waldenstrom macroglobulinemia	3 (1.60%)	0
MDS	8 (4.26%)	0
Aplastic anemia	13 (6.91%)	0
Other	16 (8.51%)	0

Treatments Received

	Control Group (n = 188)	Septic Shock Group (n = 7)
Chemotherapy causing leukopenia	41 (21.81%)	4 (57.14%)
Chemotherapy not causing leukopenia	17 (9.04%)	0
Received allogeneic stem cell transplant	27 (14.36%)	1 (14.29%)
Received autologous stem cell transplant	39 (20.74%)	0
Admission for neutropenic surveillance or became leukopenic during admission	37 (19.68%)	2 (28.57%)
Admission for GVHD	6 (3.19%)	0
Other	21 (11.17%)	0

Table 2 Multivariate Logistic Regression Final Model for Vital Signs

Vital sign	Odds ratio for septic shock	p-value	
Initial systolic blood pressure	1.070 for every decrease in 1 mmHg of systolic blood pressure	p = 0.0876	
Change in systolic blood pressure from initial value	1.060 for every decrease in 1 mmHg from initial systolic blood pressure	p < 0.05	*
Initial heart rate	1.065 for every increase in 1 bpm of heart rate	p < 0.05	*
Change in heart rate from initial value	1.052 for every increase in 1 bpm from initial heart rate	p < 0.05	*
Initial respiratory rate	2.422 for every increase in 1 bpm of respiratory rate	p < 0.05	*
Initial temperature	4.796 for every increase in 1 degree Celsius of temperature	p = 0.60	
Change in temperature from initial value	4.014 for every increase in 1 degree Celsius from initial temperature	p < 0.01	**
Age	1.106 for every increase in 1 year of age	p < 0.001	***

Table 3 Multivariate Logistic Regression Final Model for Lab Values

Lab value	Odds ratio for septic shock	p-value	
Initial sodium	1.738 for every increase in 1 mmol/L of sodium	p = 0.134	
Change in sodium from initial	2.464 for every increase in 1 mmol/L from initial sodium	p < 0.001	***
Initial potassium value	131.2075 for every decrease in 1 mmol/L of potassium	p < 0.05	*
Initial chloride	1.310 for every decrease in 1 mmol/L of chloride	p = 0.348	
Change in chloride from initial value	1.521 for every decrease in 1 mmol/L from initial chloride value	p < 0.05	*
Initial total CO2 value	1.024 for every increase in 1 mmol/L of total CO2	p = 0.940	
Change in total CO2 value from initial value	1.584 for every decrease in 1 mmol/L from initial total CO2	p < 0.05	*
Initial WBC value	1.051 for every increase in 1 x 10E3/uL of WBC	p = 0.065	
Change in WBC value from initial value	1.057 for every increase in 1 x 10E3/uL of WBC from initial value	p = 0.187	
Initial hemoglobin	1.875 for every increase in 1 g/dL of hemoglobin	p = 0.332	
Change in hemoglobin from initial value	2.042 for every decrease in 1 g/dL from initial hemoglobin	p < 0.05	*
Initial platelet count	1.032 for every decrease in 1 x 10E3/uL of platelets	p = 0.187	
Change in platelet count from initial value	1.030 for every decrease in 1 x 10E3/uL of platelets	p = 0.211	
Age	1.050 for every increase in 1 year of age	p = 0.147	

Table 4 Vital Signs Joint Modeling

Vital sign	Hazard ratio for septic shock	p-value
Diastolic blood pressure	1.27 for every decrease in 1 mmHg of diastolic blood pressure	$p < 0.01$ **
Systolic blood pressure	1.187 for every decrease in 1 mmHg of systolic blood pressure	$p < 0.01$ **
Heart rate	1.1.07 for every increase in 1 bpm of heart rate	$p < 0.01$ **
Respiratory rate	2.016 for every increase in 1 bpm of respiratory rate	$p = 0.0642$

Table 5 Multivariate Logistic Regression Final Model for Lab Values with Appropriate Logarithmic Transformations

Lab value	Odds ratio for septic shock	p-value
Initial sodium	1.307 for every increase in 1 mmol/L of sodium	p = 0.583
Change in sodium from initial	2.491 for every increase in 1 mmol/L from initial sodium	p < 0.001 ***
Initial potassium value	289.6519 for every decrease in 1 mmol/L of potassium	p < 0.05 *
Initial chloride	1.229 for every decrease in 1 mmol/L of chloride	p = 0.507
Change in chloride from initial value	1.426 for every decrease in 1 mmol/L from initial chloride value	p < 0.05 *
Initial total CO2 value	1.273 for every increase in 1 mmol/L of total CO2	p = 0.400
Change in total CO2 value from initial value	1.671 for every decrease in 1 mmol/L from initial total CO2	p < 0.05 *
Ln(Initial WBC value)	4.803 for every increase in ln(1 x 10E3/uL of WBC)	p = 0.051
Change in WBC value from initial value	1.058 for every increase in 1 x 10E3/uL of WBC from initial value	p = 0.274
Initial hemoglobin	1.936 for every increase in 1 g/dL of hemoglobin	p = 0.362
Change in hemoglobin from initial value	2.287 for every decrease in 1 g/dL from initial hemoglobin	p < 0.05 *
Ln(Initial platelet count)	1.478 for every decrease in ln(1 x 10E3/uL of platelets)	p = 0.700
Change in platelet count from initial value	1.005 for every decrease in 1 x 10E3/uL of platelets	p = 0.447
Age	1.053 for every increase in 1 year of age	p = 0.099

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