Impact of Tissue Oxygenation on Mortality in Patients with Sepsis

CSE 6242 Data & Visual Analytics Project Final Report

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***Abstract*—The purpose of this study is to determine the association between oxygen tissue extraction and mortality for patients with sepsis over a period of 30 days. When sepsis is accompanied by conditions in which systemic oxygen delivery does not meet tissue oxygen demands, tissue hypoperfusion begins, which is the inadequate perfusion of body tissues, resulting inadequate supply of oxygen and nutrients to the body tissues. It leads to oxygen debt, cellular injury, organ dysfunction and death. By being able to determine the relationship between tissue oxygenation and mortality and subsequent use of mechanical ventilation, we aim to develop mortality prediction models, which is a common metric in critical care research.**

Keywords-component: Pulse Oximetry, Central Venous Oxygen, Tissue Oxygenation, Sepsis

I. Introduction *(Motivation)* Survey

- *What are we trying to do?*

Patients in intensive care unit (ICU) are in high states of infection, which results in increased oxygen consumption by their bodies to create energy. Consequentially, tissues may resort to anaerobic metabolism[1] that leads to lactic acid production. Serum lactic acid[2] levels have been associated with mortality for sepsis patients [1]. Researchers have found that elevated lactate levels in bloodstreams influence mortality. The detrimental effects of tissue hypoxia[3] allow us to probe into areas that can help doctors monitor oxygen absorption. This study aims to correlate periodically measured levels of lactate with mortality in ICU patients.

Given the adverse effects of low oxygenation, it is crucial to improve them [2]. Studies have been conducted to improve oxygenation by modifying capillary flows. The study, however, only mentions about improving oxygenation but not about setting an upper bound, which we will evaluate as well.

Oxygen tissue extraction is computed from the difference between:

1. Pulse oximetry (SpO_2) : predicts oxygen saturation to hemoglobin in arteries
2. Central venous oxygen saturation ($ScvO_2$): measures oxygen saturation to hemoglobin in veins

Researchers have ascertained that increasing the difference between the two measurements would increase oxygen delivery to tissues [3] and could potentially reduce mortality [4]. Researchers have highlighted the importance of

[1] **Anaerobic metabolism** is the creation of energy through the combustion of carbohydrates in the absence of oxygen. This occurs when your lungs cannot put enough oxygen into the bloodstream.

[2] **Serum lactic acid** is the amount of lactic acid in a person's blood.

[3] **Hypoxia** can result from a failure at any stage in the delivery of oxygen to cells.

considering these metrics but claim that relying on SpO_2 or $ScvO_2$ individually could lead to "false reassurance" [5][6]. Thus, it is paramount to draw a relation considering both factors, which we hope to accomplish.

II. Problem Definition

Researchers have studied optimal ways of oxygen delivery to critically ill patients [7]. While they highlight the difficulty for doctors to calculate oxygen consumption and decide on treatment, they highlight the need for mathematical models with ever-growing data to make necessary deductions, which we have incorporated in our models.

Among a cohort of sepsis patients, we aim to determine the association between oxygen tissue extraction and mortality at 30 days. This can help determine if septic shocks[4] are due to low oxygenation and if additional medications are required.

III. Survey

- *Current Practices - How is it done today? What are the limits of current practice?*

Currently, various clinical metrics are used in conjunction with scoring calculators such as APACHE II, SAPS II, and SOFA to predict mortality in sepsis patients [8]. In addition to performing poorly in isolation, studies have shown that restrictive bias of these scores causes a significant difference between analyzed and predicted mortality rates [9]. Thus, by virtue of our project, we will derive insights which will help clinicians identify patients with highest risks.

- *Impact - Who cares? If we are successful, what difference and impact will it make, and how do we measure them?*

The magnitude of the problem can be seen from the following statistics:

- Sepsis Patients (U.S.): 1.5 million[5]
- Sepsis Patients (World): 26 million[6]
- Annual Mortality (US): 25,000[4]
- Annual Sepsis Increment (World): 8 - 13%[7]

Our analysis will assist in:

- Identifying septic patients with highest risk of mortality
- Efficiently allocating medical resources
- Advancing the field of medical research
- Saving lives of many sepsis patients

The impact will be measured by:

- Surveying qualitative improvement on identifying critical patients
- Number of lives saved post-study

- *Risk Assessment & Payoffs - What are the risks and payoffs? How much will it cost?*

Risks: 1. Equipment Related Errors - Researchers have studied how external factors, like sensors could impact $ScvO_2$ readings [10]. However, the study also mentions that this risk can be considered negligible as they do not significantly impact healthcare maneuvers. 2. Medical Condition of Subject: Studies have shown that conditions, like anaemia[8], can cause $ScvO_2$ to decrease, while conditions like oedema[9] can cause it to increase. Researchers have ascertained this by using a range instead of a threshold [11]. This mitigates the effect of the risk in our project.

Payoffs: The association we aim to find between tissue oxygen extraction and mortality can:

- Help in medical resource allocation
- Be used to predict mortality in critical care research
- Clear speculations in the context of tissue level oxygen absorption

These payoffs help us arrive at an optimal range, which is difficult to accomplish towards later stages of sepsis [12][13]. Given a good range of $ScvO_2$ values, clinicians will be able to perform better treatment for patients.

Cost: The project's goal will be accomplished by expending human effort (utilizing data preprocessing and visualization techniques) and without monetary costs.

IV. Proposed Method

- *What's new in your approach? Why will it be successful?*

[4] **Septic shock** is a life-threatening condition that can occur as a complication of sepsis.
[5] **CDC** (2017). Retrieved from: https://www.cdc.gov/sepsis/datareports/index.html
[6] **Sepsis Fact Sheet** (2016). https://www.sepsis.org/downloads/2016_sepsis_facts_media.pdf
[7] **World Sepsis Declaration** (2017). https://www.world-sepsis-day.org/declaration/

[8] **Anaemia** is a condition that develops when blood lacks enough healthy red blood cells or hemoglobin.
[9] **Oedema** is a buildup of fluid in the body which causes the affected tissue to become swollen.

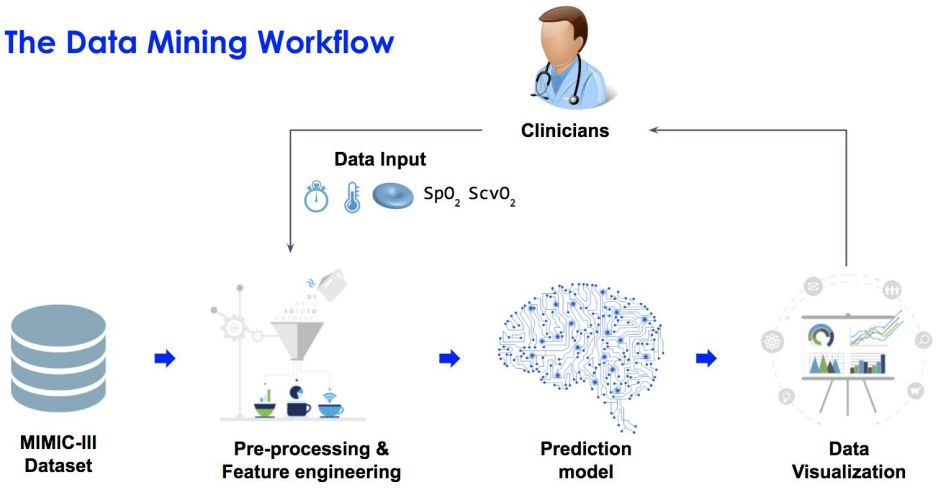

Figure 1: Data Mining Workflow

Novelty in Method, Innovation, Better than State of the Art: Across literature, researchers focus on association of compounds with $ScvO_2$ levels or $ScvO_2$ concentrations across time to study the impact on criticality of patients [14][15], but there has not been any study on time-dependent correlations of other compounds with $ScvO_2$ levels that can be helpful to study the impact on patient-criticality. Although there is a study about mortality prediction using machine learning [16], the researchers used hundreds of variables while we plan to use time-dependent variables having significant correlation. In our model, we aim to capture variation and prolonged impact of spikes in values using time component of features and time series analysis. In addition, we perform feature engineering by building new features at every time step, which gives more information about data trends for the model to learn.

Why We Believe It Would Work: Since our approach combines both features' interaction and their time-variation with response [17], we hope to better deduce the association of mortality with features like oxygen extraction in tissues, and help doctors take better, informed decisions.

Description of approach, algorithms, and user interfaces: We plan to pre-process ICU patients data obtained from MIMIC-III[10] database by selecting features that are pertinent to our project: Pulse Oximetry (SpO_2), Central Venous Oxygen ($ScvO_2$), Temperature, pH, Lactate, and Haemoglobin for each timestamp at which $ScvO_2$ levels were measured. Upon building the data, we tag each instance with the boolean value indicating if the patient survived the next 30 days.

At each timestep, we engineer new features to determine momentum, moving average, and standard deviation so that we capture how the attribute values change over a window of last 2-7 observations. This allows us to capture the slightest changes in values. Monitoring these trends will more accurately impact the mortality of patients over 30 days.

We have tried standard classification Machine Learning models on the dataset such as Xgboost, Support Vector Machine (SVM), Logistic Regression, and Random Forest. The data was split into train (80%), and test (20%) data sets. 10-fold cross validation was done on the training set to hypertune the model parameters, and the tuned model's performance was evaluated on the test set. Xgboost had the best performance and was chosen for mortality prediction analysis.

The user interface is designed to allow doctors upload CSV files containing the relevant attribute values of patients. The file is then used as the test set on which the saved model files (generated from training set) in backend are used to make predictions of mortality scores [18]. This will allow doctors to observe, analyze, and attend to patients who are at the highest risks of mortality.

[10] **MIMIC-III** (Medical Information Mart for Intensive Care III) is a large, freely-available database comprising identified health-related data associated with over forty thousand patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012.

pID	Time	ScVO2	SpO2	Temp	pH	Lactate	Hb	If-Dead [0/1]
P1	t11	x11	y11	T11	pH11	L11	Hb11	
P1	t12	x12	y12	T12	pH12	L12	Hb12	
P1	t13	x13	y13	T13	pH13	L13	Hb13	
P2	t21	x21	y21	T21	pH21	L21	Hb21	
P2	t22	x22	y22	T22	pH22	L22	Hb22	
P3	t31	x31	y31	T31	pH31	L31	Hb31	
P3	t32	x32	y32	T32	pH32	L32	Hb32	
P3	t33	x33	y33	T33	pH33	L33	Hb33	
P3	t34	x34	y34	T34	pH34	L34	Hb34	
P3	t35	x35	y35	T35	pH35	L35	Hb35	

pID	momentum	moving avg.	SD	.....
P1	0	0	SD1	...
P1	0	(pH12+pH11)/2	SD1	...
P1	(pH13/pH11)-1	(pH13+pH12)/2	SD1	...
P2	0	0	SD2	...
P2	0	(pH22+pH21)/2	SD2	...
P3	0	0	SD3	...
P3	0	(pH32+pH31)/2	SD3	...
P3	(pH33/pH31)-1	(pH33+pH32)/2	SD3	...
P3	(pH34/pH32)-1	(pH34+pH33)/2	SD3	...
P3	(pH35/pH33)-1	(pH35+pH34)/2	SD3	...

Figure 2: Feature Engineering

V. Design of Experiments / Evaluation

The objective of the experiment is to determine associations between tissue oxygen extraction and mortality using time-series analysis and machine learning classification models. We also aim to determine how other confounders such as pH, hemoglobin, lactate and temperature impact the mortality and observe patterns in their trends for sepsis patients.

In the time series analysis, we engineered additional features such as moving averages, standard deviation and momentum for modelling the multivariate time series data. The moving average helps capture prolonged impact of spikes; momentum captures impact of change per unit time on response; and standard deviation captures association of feature-variation with response.

Although these features seemed promising in the beginning, they did not add much value in terms of predictive power of mortality. One of the possible reasons for this was that the predictors we used were recorded in very short intervals, while the predictions were being made for 30 days (input from the doctors). Hence, there was not a significant change in the response variable (mortality) that we observed because of change in predictors.

Coming to the dataset, we had 330 million rows, and is unique at patient/timestamp level. After filtering out the patients with sepsis who were admitted in ICU, we were left

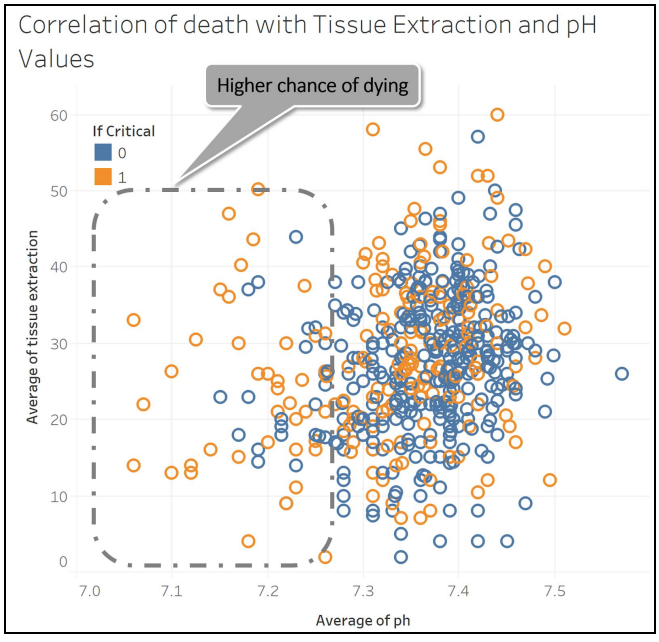

Figure 3: Relation of Tissue extraction and pH with death rate

left with ~10,000 records. Out of those patients, the $SCvO_2$ values were available only for ~5,500 records, which was our final dataset - it contained records 528 unique patients. The death rate in our data was ~35%, which complies with the statistics available for death rate of septic patients.

After analyzing the data, we found out that sepsis patients having lower pH value and higher lactate values have a higher chance of dying within 30 days of diagnosis tests as compared to the patients that have higher pH and lower lactate values as seen from Figure 3**.**

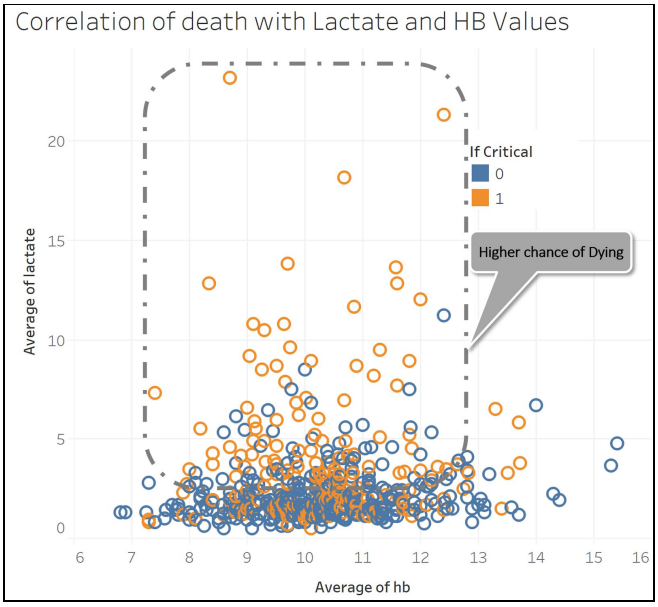

Figure 4: Relation of lactate and HB with death rate

We also found out that the average tissue extraction values for patients at later observations are lower for the patients who died within 30 days of diagnosis, as compared to those who didn't. The trend is surprisingly opposite at the beginning as seen from the Figure 5.

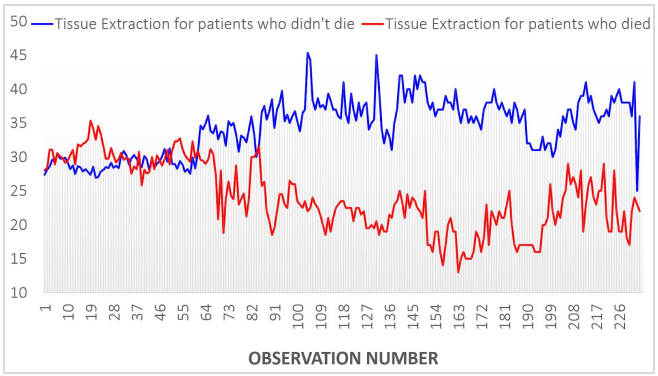

Figure 5: Trend of Tissue extraction with observation number

- *Experiment Results*

We first built classification models using the Logistic Regression, Support Vector Machines, Random Forest, Light GBM and XG-Boost using 80% of data as train and 20% of data as test. For evaluation, we used Area Under Curve (AUC) for ROC, F-Score, Precision, Recall, and Test data accuracy. A better performing model would be expected to have a higher AUC and Recall [since we want to capture patients who would die with more accuracy].

Below is the table highlighting the performance of each model.

	Logistic Regression	Support Vector Machine	Light GBM	Random Forest	XG Boost
AUC	56.6	62.8	78.7	81.0	81.4
F-Score	26.67	43.1	72.2	75.2	72.5
Test Accuracy	72.1	75.3	81.4	86.4	80.5
Precision	68.3	73.6	82.1	85.3	63.9
Recall	16.6	30.5	68.9	70.7	83.7

Table 1: Model Performance - Initial

To improve on the results, we used 10-fold cross validation and grid-search to finetune the model parameters, with the objective of maximizing the AUC-score. Below are the results with optimized parameters.

	Logistic Regression	Support Vector Machine	Light GBM	Random Forest	XG Boost
AUC	60.9	69.3	81.2	82.7	83.5
F-Score	46.5	57.5	75.2	77.3	77.9
Test Accuracy	65.6	73.0	85.1	87.3	87.0
Precision	44.5	55.5	83.2	85.3	81.5
Recall	48.8	59.8	68.1	70.7	74.6

Table 2: Model Performance - Final

We see a significant jump in the AUC values, specifically for Logistic regression and SVM that were not performing well initially as seen in Figure 6. Despite the improvement, XG-Boost and Random forest still outperformed the rest, with an AUC of ~84%, F-score of ~78%. We decided to use XG-Boost for mortality prediction because of a higher recall value of 74.6%.

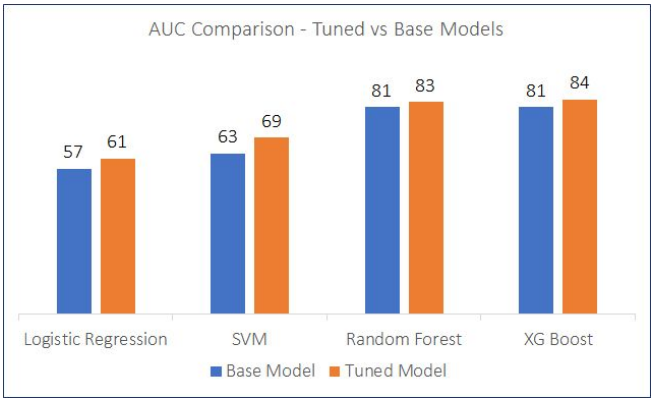

Figure 6: Tuning model parameters to improve performance

- *Evaluation*

As analyzed above, we saw that higher lactate and lower pH values contribute to a higher death-rate. This was validated by the XG-Boost parameter importance in terms of f-score, which is highlighted below.

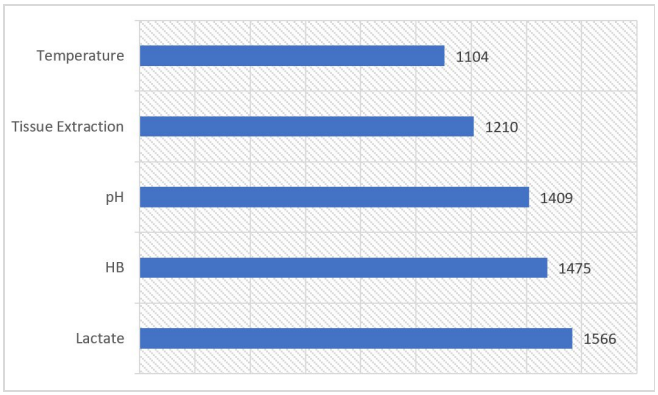

Figure 7: Variable importance in terms of F-score for XG-Boost model

We also realize that there is no significant impact of tissue-extraction on mortality of sepsis patients as observed from the variable-importance score. However, the doctors were interested in determining the relationship that tissue oxygen extraction had with mortality. As seen in Figure 5, we were able to observe a decreasing trend for patients who died. The oxygen extraction was steadily declining and patients who did not survive had a lower oxygen tissue extraction compared to those who did survive.

For an unseen data (20%, 1,115 records), we see the the confusion matrix of prediction-model and distribution of patient criticality in Fig. 8 and Fig. 9 respectively .

Confusion Matrix - XG Boost	Death Predicted	Death Not Predicted
Patients Died	252	86
Patients Didn't Die	70	707

Figure 8: Confusion matrix for XG-Boost

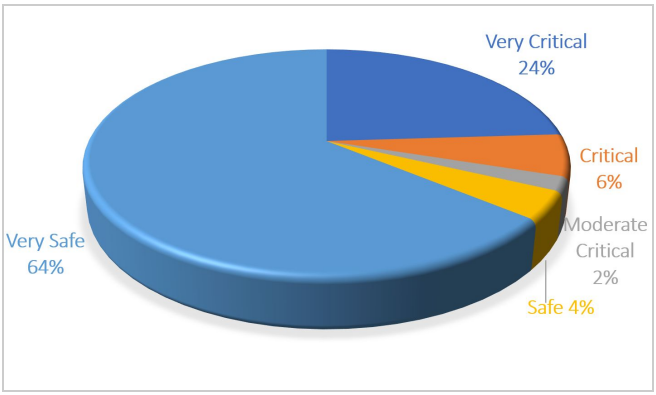

Figure 9: Distribution of patient-criticality on unseen data

VI. Plan of Activities

- *How long will it take? What are the midterm and final exams for success?*

The midterm goals initially set were achieved. The goals entailed data cleaning, preprocessing, and preliminary analysis together with frontend development.

For the "final exam", we had wanted to further tune the models and improve performance in addition to determining the effects of external confounders on the mortality of ICU patients. We have also developed a complete pipeline that involves processing input data given by clinicians, evaluating them based on the prediction model, and giving mortality prediction values to doctors. We have a developed a prototype that is ready for the doctors to use for lab test result analysis. We hope these results and tools will aid doctors and contribute towards saving more lives.

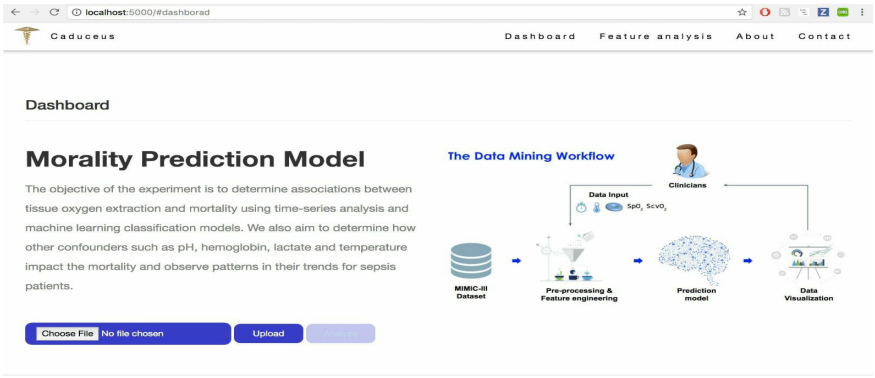

Figure 10: Frontend UI

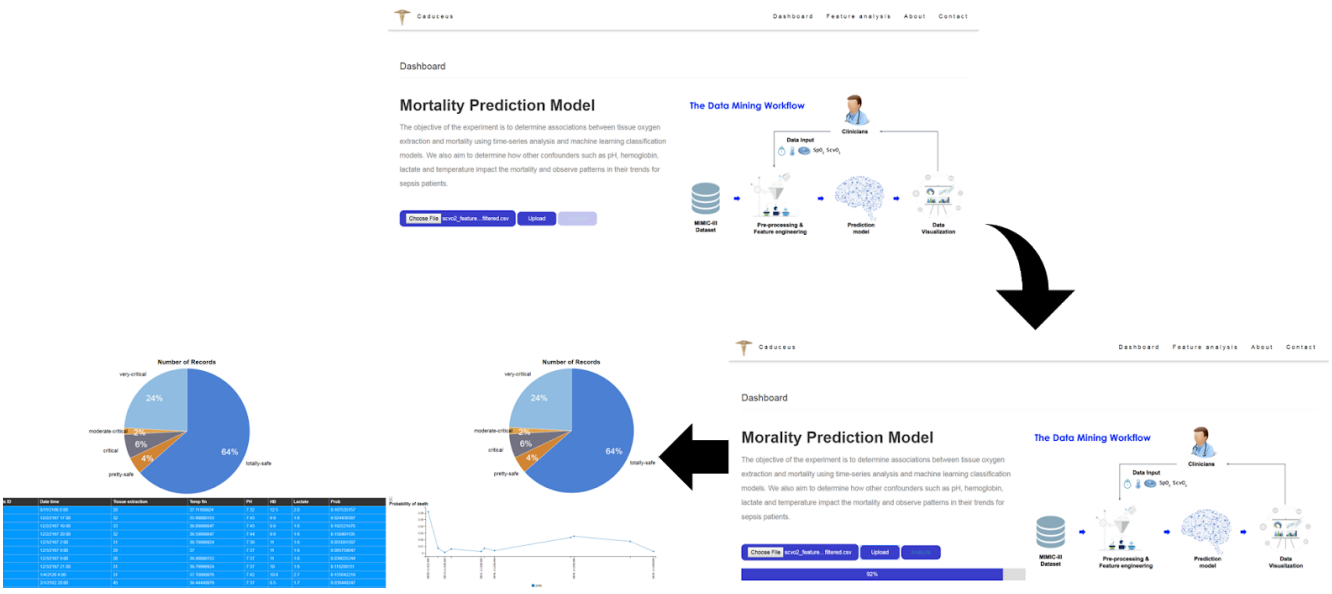

Figure 11: Fronted UI demonstration

VII. Conclusion & Discussion

In conclusion, we believe our analysis will help further critical care research and aid clinicians in identifying patients with highest risks in ICU. In doing so, we hope to reduce the number of deaths as more resources and attention is given to them early.

Future Work: We plan to further improve the prediction models by performing dimensionality reduction using Principal Components Analysis, and feature selection using Information Gain. We plan to migrate the data and codebase to Amazon EC2 instances so as to parallelize and speed up data preprocessing and develop an efficient workflow.

We aim to develop front-end visualizations on the dashboards for the doctors to get key metrics and scores in addition to giving mortality predictions for the given ICU patients data.

VIII. Team Member Work Distribution

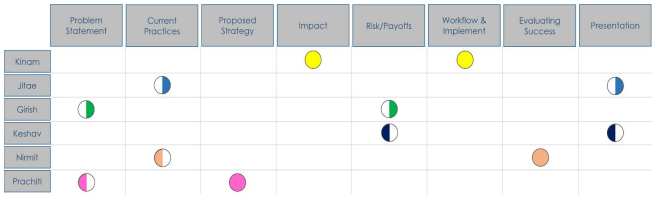

Figure 12: Equal Work distribution for Report Analysis

Figure 13: Equal Work distribution for Code Implementation

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