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Statistical and Prognostic Modeling of Clinical Outcomes with Complex Physiologic Data

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Statistical and Prognostic Modeling of Clinical Outcomes with Complex Physiologic Data in Intensive Care Unit Patients

by

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DEDICATION

This dissertation is dedicated to my family, particularly my husband, Sandro, who has supported me during these years, and to my wonderful kids, Omar and Dana, who are the reasons for and the joy of our lives.

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I would like to thank my advisors Dr. Jose Luis Zayas–Castro and Dr. Peter J. Fabri for their continuous support and guidance during this process. I have really enjoyed working with them and learning from their experiences. I also would like to thank my family for their support during these years.

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ABSTRACT

Laboratory tests are a primary resource for diagnosing patient diseases. However, physicians often make decisions based on a single laboratory result and have a limited perspective of the role of commonly-measured parameters in enhancing the diagnostic process. By providing a dynamic patient profile, the diagnosis could be more accurate and timely, allowing physicians to anticipate changes in the recovery trajectory and intervene more effectively.

The assessment and monitoring of the circulatory system is essential for patients in intensive care units (ICU). One component of this system is the platelet count, which is used in assessing blood clotting. However, platelet counts represent a dynamic equilibrium of many simultaneous processes, including altered capillary permeability, inflammatory cascades (sepsis), and the coagulation process. To characterize the value of dynamic changes in platelet count, analytical methods are applied to datasets of critically-ill patients in (1) a homogeneous population of ICU cardiac surgery patients and (2) a heterogeneous group of ICU patients with different conditions and several hospital admissions.

The objective of this study was to develop a methodology to anticipate adverse events using metrics that capture dynamic changes of platelet counts in a homogeneous population, then redefine the methodology for a more heterogeneous and complex dataset. The methodology was extended to analyze other important physiological parameters of the circulatory system (i.e.,

calcium, albumin, anion gap, and total carbon dioxide). Finally, the methodology was applied to simultaneously analyze some parameters enhancing the predictive power of various models.

This methodology assesses dynamic changes of clinical parameters for a heterogeneous population of ICU patients, defining rates of change determined by multiple point regression and by the simpler fixed time parameter value ratios at specific time intervals. Both metrics provide prognostic information, differentiating survivors from non-survivors and have demonstrated being more predictive than complex metrics and risk assessment scores with greater dimensionality.

The goal was to determine a minimal set of biomarkers that would better assist care providers in assessing the risk of complications, allowing them alterations in the management of patients. These metrics should be simple and their implementation would be feasible in any environment and under uncertain conditions of the specific diagnosis and the onset of an acute event that causes a patient's admission to the ICU.

The results provide evidence of the different behaviors of physiologic parameters during the recovery processes for survivors and non-survivors. These differences were observed during the first 8 to 10 days after a patient's admission to the ICU. The application of the presented methodology could enhance physicians' ability to diagnose more accurately, anticipate changes in recovery trajectories, and prescribe effective treatment, leading to more personalized care and reduced mortality rates.

CHAPTER 1: INTRODUCTION

1.1 Background

One of the major concerns of the U.S. government is the situation of the healthcare system. There are several factors associated with this issue, and some have motivated the development of this research: (1) the current level of healthcare cost in the U.S., (2) the availability of massive datasets, (3) the lack of effective tools to help healthcare providers improve their diagnoses and the interpretation of results, and (4) high mortality rates. It is estimated that National Health Expenditures (NHE) currently are approximately 18 percent of GDP ($2.9 trillion), and they are expected to reach 19.9 percent by 2022 ($5.0 trillion) [1]. This concern is shared by both the private and public sectors, since U.S. government spending is approximately 20 percent of GDP [2]. The rapid advancements in healthcare information technology have led to massive and heterogeneous datasets. However, the amount of information that is currently extracted from those datasets is limited due to the complexity of health processes and the lack of tools to assist physicians in better analyzing and interpreting results. Physicians are usually not trained to simultaneously analyze multiple attributes and, often, their decisions are made based on the last test result as a last picture of the patient compared to "normal" ranges and their experience. The high mortality rates faced by U.S. hospitals are also an important issue. Cardiovascular diseases and post-surgical health management are two of the primary causes of death in U.S.: in general, 10–29 percent of patients admitted to adult intensive care units (ICUs)

die in hospitals across the U.S. [3], and 23.7 percent of total deaths are caused by heart disease, which continues being the leading cause of death [4].

The accurate assessment of the circulatory system is important for all critically-ill patients. Often, changes in circulatory status occur rapidly, with possible complications for the patient, and interventions and decisions have to be made as early as possible. Laboratory tests are the primary resource for diagnosing patient diseases and monitoring critically-ill patients. However, physicians often make decisions based on a single laboratory result, ignoring important factors such as patient historical test results and the relationships among different types of tests. They have a limited perspective of the role of commonly-measured parameters from the Complete Blood Count (CBC) test and the Basic Metabolic Panel (BMP) test and their interactions and changes over time. The CBC provides information regarding the types and number of cells in blood, and the BMP provides information about glucose, electrolytes, and fluid balance.

There is a need to provide physicians with a dynamic patient profile and to develop methodologies and tools to assist (1) the extraction of pertinent knowledge from common and less expensive healthcare records (e.g., lab test results), (2) the anticipation of postsurgical adverse events, and (3) the provision of more personalized patient care. This study focused on modeling and analyzing multiple physiologic parameters, looking for a minimal set of markers that could assist physicians in timely identifying and assessing the risk of adverse events.

The principal components of the blood are white blood cells, red blood cells, platelets and plasma, and platelets. The most common cells in the human body are red blood cells. They help the system in delivering oxygen (O_2) to body tissues and carrying carbon dioxide (CO_2) to the lungs to be exhaled. A reduced level of red blood cells, known as anemia, is the most common

disorder, which may lead to different clinical consequences. Plasma is a liquid that carries all the blood cells in suspension. It transports dissolved salts, proteins, nutrients, hormones, clotting factors, and electrolytes throughout the body as necessary. It also helps to remove waste products from the body. White blood cells help the body in fighting infectious diseases, attacking and destroying any bacteria or organism that causes the infection. Platelets are cells that bind and react to damaged blood vessels. They are related to the clotting of blood and prevention of bleeding. Therefore, platelets are relevant in heart attacks, strokes, and peripheral vascular diseases. A platelet count is the amount of platelets in the body. Too many or too few platelets may cause varied disorders. However, platelets can also present abnormalities in their function, which may lead to other disorders.

There are also other physiologic parameters measured through blood tests that have been demonstrated to provide prognostic information. Two of them are albumin and calcium. Albumin is one of the main proteins of plasma. It is a component of acute injury response and decreases in response to inflammation. Therefore, it is also known as a negative acute phase reactant. It has been demonstrated to be a proper predictive marker of surgical complications, and low levels of albumin have been found in patients who have major sepsis (a very severe inflammation of the whole body, commonly caused by severe infection). Additionally, several studies have suggested that albumin level can be an independent predictor of mortality in different clinical settings.

Calcium is an important mineral in the human body. Blood calcium level is also a common test conducted as part of a basic metabolic panel test. Usually, it is measured when a patient presents symptoms suggesting kidney stones, bone disorders, or neurologic disorders. Blood calcium also has shown to be related to critically-ill patients, and some studies have

suggested that alterations in calcium levels occur frequently in the ICU patient population. The use of these and other parameters as markers are reviewed in Chapter 2 of this dissertation.

1.2 Research Objectives

This research aims to develop a generalizable methodology to assess dynamic changes of specific clinical parameters for a heterogeneous population of ICU patients, using rate of change and developing an index able to provide valuable information to anticipate adverse outcomes.

The specific objectives of this research are to (1) develop a methodology to anticipate patient outcomes using dynamic changes in platelet count in a homogeneous population, (2) apply to a heterogeneous and complex dataset to determine the ability to generalize the results to a broader population, (3) extend the methodology to other parameters such as mean platelet volume, albumin, and calcium with the homogeneous dataset, and (4) generalize the methodology analyzing simultaneously specific parameters from a heterogeneous dataset.

1.3 Organization

This document is organized as follows:

- Chapter 2 is a relevant literature review regarding common blood tests for patient monitoring, current practices associated with the analysis of laboratory test results, and monitoring techniques of patient recovery processes. Specific studies that use platelet count and calcium as markers are also presented, and the use of anion gap, total carbon dioxide, and albumin as parameters that can provide prognostic information is reviewed.

- Chapter 3 presents the methodology applied, including a detailed description of the datasets and their construction, the study protocol, and details of the comparison of the two datasets selected. The statistics used to evaluate and validate the models are presented. These statistics allow the comparison of the models' performance with the performance of other models from previous studies using similar physiologic parameters.
- Chapter 4 presents the results for each step described in the methodology section and a discussion regarding the relevance of the results and their comparison with previous studies using physiologic data.
- Chapter 5 includes conclusions, contributions, and the limitations of the research, as well as guidelines regarding further investigation to validate the results to be applicable for new ICU patients.

CHAPTER 2: LITERATURE REVIEW

This chapter has four main objectives. First, it describes the basic hemodynamic parameters used to monitor patients during ICU patient recovery trajectories and their application in different studies as possible prediction markers of patient outcome. Second, it discusses the current practice associated with laboratory test analysis, as well as current practices in patient monitoring. Third, a detailed literature review in the use of platelet count as a predictor of patient outcome is discussed. The final section reviews the use of other physiologic parameters as part of patient monitoring.

2.1 Common Blood Tests for Patient Monitoring

Laboratory tests are a primary resource for diagnosing patient diseases and assessing patient progression. The most common tests ordered are the basic metabolic panel (BMP) and the complete blood count (CBC) test. The BMP is usually ordered as a routine medical exam. However, in critically-ill patients, the test can suggest medical causes of fluid imbalances that may require immediate intervention. The CBC is also a routine health laboratory test, but in critically-ill patients it provides information regarding disorders that affect blood cells. It is also performed to determine the effectiveness of treatments. Some therapies or medications can affect the production of cells, and a CBC is usually ordered to help monitor the treatments.

2.1.1 Basic Metabolic Panel (BMP)

A BMP is a group of blood tests that provide information about the patient's metabolism. It is usually conducted to evaluate how the kidneys are functioning regarding blood fluid balance and blood sugar levels by measuring the levels of sodium, potassium, chloride, carbon dioxide, total bilirubin, total protein, glucose, creatinine, blood urea nitrogen (BUN), and calcium [5]. Blood sugar levels are measured in terms of glucose, one of the energy sources of the body. Fluid balance is measured in terms of electrolytes (potassium, calcium, and sodium). All contribute to the proper functioning of the nerves and muscles in the body. Creatinine and blood urea nitrogen are both waste products filtered by the kidneys. Their test results provide information on how well the kidneys are functioning. Abnormal results may be due to diverse conditions. These medical conditions may include kidney failure, diabetes, liver disease, breathing disorders, and side effects of medications [6].

2.1.2 Complete Blood Count (CBC)

A CBC is commonly ordered to monitor disease progression with response to a treatment or as a routine checkup [7] for symptoms such as weakness, fatigue, or bruising [8]. A CBC provides information about the white blood cells, red blood cells and platelets. This test measures the number of white blood cells (WBC count), the number of red blood cells (RBC count), the fraction of the blood composed of red blood cells (hematocrit), and the total amount of hemoglobin in the blood. The test also provides information about the average red blood cell size (MCV), hemoglobin amount per red blood cell (MCH), the amount of hemoglobin relative to the size of the cell (hemoglobin concentration) per red blood cell (MCHC), and platelet count [8].

As described previously, all blood cells have different functions in the circulatory and immune systems (oxygen transport, blood clotting, infection and inflammation fighting) and, depending on their levels (low or high), diverse blood disorders with clinical consequences may appear. This test may provide physicians support in the diagnosis of allergies or diverse infections, detection of blood clotting problems or blood disorders such as leukemia or anemia, and the evaluation of red blood cell production or destruction [8].

2.2 Current Practice in the Analysis of Laboratory Test Results

The blood tests previously mentioned are the most common tests ordered to monitor patients and diagnose diseases. However, depending on the disease, physicians could order additional tests to confirm or discard any initial findings. This situation is more critical while assessing a patient's progression in high-risk populations as ICU patients or patients suffering from chronic diseases. In these cases, more information is needed to make effective early decisions given the patient's condition and the associated risks. Care providers usually assess laboratory results by comparing them with "normal ranges," which are based on specific healthy populations or on limits that characterize a specific medical condition. Moreover, these ranges depend on the methodology used to determine them; there is no standard methodology [9]. In addition, another issue is the difference across laboratories. Clinical laboratories use different techniques and methods to obtain results. Techniques, methods, and equipment are subject to various sources of variability, from calibration to materials to human skills. A study demonstrated that the severity of metabolic acidosis depends on the bicarbonate assay used. The study concluded that the recognition of these differences is relevant for the definition of the severity of metabolic acidosis and the corresponding treatment [10].

Another important factor to consider is the variability among patients, even if they are part of a homogeneous population. The behavior of physiologic parameters varies among individuals; each person has her/his own "normal" ranges depending on personal conditions and characteristics. There is also variability within patients. This variability is affected by other factors in addition to the disease, such as emotional and environmental factors. For this reason, the analysis of test results should "ideally" be patient-specific. Unfortunately, the comparison of specific characteristics in a static "mode" of the patient's condition does not provide physicians with the dynamism needed to understand the patient's condition. The relationship among the results from the different tests cannot be effectively observed through static lenses. This research focuses on capturing the dynamism of specific physiologic signals through metrics that could provide useful information to the physician.

2.3 Current Monitoring Techniques of Patient Recovery Process

There are several techniques applied to monitoring patient progress. Most of them monitor patients with cardiovascular diseases, because they continue being the leading cause of death in the U.S. [4]. The principal aspects considered during monitoring are the determination of the parameters that best represent the patient's condition, the risks associated with the disease, and the modeling and prediction of patient outcomes [11, 12, 13]. The common parameters measured were described in the previous section; however, there is no agreement on which parameter—or set of parameters—can better describe a patient's condition.

Many previous studies focused in using clustering methods to segregate the population, looking for similarities among patient characteristics. Some clustering methods have been modified to be applicable to dynamic environments (e.g., k-means or agglomerative hierarchical

method) for specific purposes such as fuzzy logic-clustering. One study applied a fuzzy logic clustering method for functional magnetic resonance imaging (fMRI) for the detection of brain activation during the application of a stimulus [14]. However, laboratory sampling procedures are not standard and samples are not taken at specific intervals. Thus, time series analysis has been used to analyze data dynamically, and clustering time series data have been used in various application domains [15]. Taking into account the development of healthcare information technology and the increment of healthcare data registered, the interest in temporal data mining research has increased. The principal difference between a static and a dynamic time series is the methodology used to measure the similarities between two patients or data objects.

Time series has been also applied in detecting influenza epidemics [16] and modeling influenza incidence [17]. Nevertheless, to apply times series, the sample size takes an important role and, depending on the time frame, sometimes the values assigned to the parameter of interest, which are averaged values, are not representative of the real values associated with the time series. This issue is more important in the case of physiologic parameters, because their changes or variability over time are high due to different factors, and the samples are taken by request of the physicians and not on a regular basis. For example, in the case of platelet counts, factors such as invasive procedures, transfusions, catheters, or platelet function defects or blood or bone marrow disorders may affect the level of platelets.

Other studies have focused on the use of Markov processes [18, 19] to model disease progression, such as infectious diseases. Peng *et al.* [20] applied sequential cluster methods to establish the classification of the infectious disease state and then presented a weighted Markov chain procedure to predict the future incidence state. However, few studies have modeled the temporal evolution of postsurgical recovery and have used laboratory test results as a primary

source. One study used multivariate time series, applying fuzzy logic methodologies to cluster patients after cardiac surgery. The multivariate clustering allowed the representation of potential risks associated with patients during their recovery process and clustering them into groups to further generate risk profiles per group [21].

2.4 Platelet Count as a Biomarker

A platelet count measures the amount of platelets in the blood. Platelets are blood cell fragments that travel in blood vessels and clot and are the smallest type of blood cell. One of the most important functions is the formation of blood clots. If a blood vessel is damaged, then the platelets clump and form a plug (called platelet aggregation) that will help stop bleeding. Platelets also contribute in inflammatory processes in tissue. They are also called thrombocytes, because a blood clot also is called a thrombus [22]. The number of platelets can be altered by diverse diseases and conditions (such as bone marrow or immunologic problems, liver disease, or some medications), and they may be counted to monitor or diagnose diseases. According to the National Institute of Health, the reference range for a platelet count is from 150,000 to 450,000 units per microliter (mcL) [23].

Abnormalities in platelet numbers and functions are coagulation disorders observed in ICU patients [24]. An abnormal drop in the number of platelets in the bloodstream, known as thrombocytopenia, may result in increased bleeding. Thrombocytopenia may be result of a deficit in platelet production, an excess in platelet destruction, or an increment of consumption in the bloodstream. Some studies have found associations between a decline in platelet counts and patient outcomes [25], whereas a decline in platelet counts for patients who stayed more than five days in an ICU provided prognostic information. Some studies have focused on platelets

recognizing that they are involved in the pathogenesis of sepsis and that the severity of sepsis correlates with the decrease in platelet counts [26]. Other studies have reported that ICU mortality is significantly higher in thrombocytopenic patients [27, 28, 29, 30].

Baughman *et al.* [27] reviewed 162 records of ICU patients and concluded that thrombocytopenia was common in ICU patients and was associated with longer hospital stays and increased mortality. This was an issue supported by Greinacher *et al.* [30], who reported that approximately 40 percent of the ICU patients had thrombocytopenia. Stephen *et al.* [28] conducted a study with 147 ICU patients with surgical intervention. The data was collected during six months and the conclusion was that thrombocytopenic patients had a higher mortality and that this condition probably was a reflection of the magnitude of an underlying pathologic condition. The authors also suggested that the correction of this condition may be an appropriate prognostic factor. Thrombocytopenia was defined as a risk factor for mortality in a study that analyzed thrombocytopenia during sepsis. The authors evaluated if this condition could predict mortality in ICU patients [29]. This study also reported that the platelet count in survivors was higher than in non-survivors.

It can be observed in all these studies that low levels of platelet count are very risky and may suggest the severity of an illness; however, an elevated number of platelets, known as thrombocytosis, could cause spontaneous blood clots, which may be risky as well. Thrombocytosis may be present due to an infection or any blood or bone marrow disorder, but, in those cases, platelets may take part in the coagulation of arteries with the possibility of causing atherosclerosis. These types of disorders also are important, because they can cause vein thrombosis, or any thrombosis that may lead to stroke or heart attack.

As mentioned, platelet disorders also could be related to their function. Platelet adhesion (to the vessel walls), aggregation, and activation may be affected in critically-ill patients. However, tests associated with measuring the ability of adhesion or aggregation are influenced by several factors and are not common. These parameters were not available in the datasets analyzed, nevertheless, it is important to note that these abnormalities exist and may affect patient clinical outcomes.

Finally, another characteristic of platelets is platelet volume, which can be estimated as part of a CBC test. Some studies have suggested that an increment in MPV may increase mortality risk in ischemic heart diseases [31].

Although it has already been recognized that "*determining trends in platelet count is of additional prognostic value compared with single measurements*" [32], none of the studies have looked in more detail at the dynamic changes in platelets, nor have they identified any specific signal or marker that can alert physicians for possible complications.

Considering the importance of platelets in monitoring ICU patients, it seems appropriate to study their behavior over time and develop a methodology to capture their change as a predictor of patient outcome. Since this behavior is critical for patients with heart disease, this research has two parts: (1) investigate a specific group of ICU patients with heart disease who underwent specific types of cardiac operations and (2) investigate a mixed population of ICU patients from different hospitals and with varied conditions. The objective is to develop a methodology to predict patient outcomes with a homogeneous cardiac dataset and then replicate or redefine the methodology for a heterogeneous and more complex dataset.

Nijsten *et al.* [33] conducted a retrospective study to analyze the relevance of time-dependent changes of platelet counts in ICU patients. The study found an association between patients with low rate of change in platelet count and mortality. The authors observed that between days 2 and 10, non-survivors had a smaller increase in platelet counts than survivors. The rate of change was calculated daily and the result was comparable with the Acute Physiology Chronic Health Evaluation II (APACHE II; [33]) score in predicting mortality, which uses the leukocyte (white blood cell) count.

Another study conducted by Akca *et al.* [35] focused on describing the changes of platelet count over time and relating them to mortality rate in critically-ill patients. This prospective study included data from 40 ICUs gathered in 16 countries. The patient population enrolled in the study included 1,449 critically-ill patients, but only 257 stayed for more than 2 weeks in the ICU. The study showed a biphasic pattern of platelet count, which was different in survivors and non-survivors, and concluded that late thrombocytopenia (platelet count less than $150x10^3/mm^3$) was a better predictor of death than early thrombocytopenia. The authors also observed that after thrombocytopenia, the platelets increase for survivors, issue that was not observed in non-survivors. They concluded that the platelet count decreased significantly in the first three days after admission, reaching a low point on day 4 for both survivors and non-survivors.

After review of these studies, it can be concluded that the analysis of changes in platelet count over time is important in critically-ill patients and may provide prognostic information. In all of the reviewed studies, thrombocytopenia was presented in critically-ill patients, suggesting that low platelet count is related to patient outcome and mortality.

The next section describes other hemodynamic parameters that have shown to be related to clinical outcomes and may also provide additional information regarding patient progression. Therefore, they may be considered for inclusion in our predictive models.

2.5 Other Parameters used to Monitor Patient Progression

Several commonly-measured parameters help physicians monitor patients. Depending on the disease and the patient's condition, the tests vary, but the primary source is blood tests. As explained, the blood has basic components, but there are other physiologic attributes measured in the blood, such as albumin and calcium, that have been demonstrated to provide prognostic information. Albumin is an important protein of blood plasma; it regulates the colloidal osmotic pressure of blood and transports hormones and fatty acids, among others. Some studies that have found that reduced levels of albumin concentration are associated with mortality risk [36]. Other studies have found that a low level of albumin (hypoalbuminemia) in patients with critical conditions is associated with poor outcomes [37, 38], and others that low albumin concentration in the blood independently predicts morbidity [39]. The impact of albumin levels in critically-ill patients has been observed and analyzed by several researchers. Most studies have observed that albumin levels decrease at the beginning of a critical illness and continue without increasing until the recovery phase [39].

Calcium is the most common mineral in the human body and one of the most important. Most calcium is found in bones, but a small amount is found in blood. Calcium affects bone and teeth building, but it also influences the nervous system and the blood clotting process. When blood calcium levels are low (hypocalcemia), calcium is extracted from the bones; when the calcium level in the blood is high (hypercalcemia), the body stores it in the bones or discards it.

Blood calcium also has shown to be related to critically-ill patients. Some studies have suggested that alterations in calcium levels occur frequently in the ICU patient population. Hypocalcemia has been reported in critically-ill patients, and decreased calcium levels have been correlated with increased mortality [40]. Another study found a drop phase in plasma calcium for patients who underwent cardiac surgery [41]. In this study, all patients were survivors, but all had a significant drop in plasma calcium, reaching a minimum during the second day after surgery. However, patients with other complications reached minimum values six days after surgery.

Two other parameters that could be explored as possible markers are the anion gap and total carbon dioxide (TCO_2). The anion gap in blood is the difference between cations (positively-charged ions) and anions (negatively-charged ions) in serum. It is a common measure used to identify the cause of metabolic acidosis, that is, a lower-than-normal pH in the blood. However, it has been used not only to diagnose acid-base disorders but also to diagnose other conditions. One study concluded that an increased anion gap at admission is a predictor of patient mortality in the critically-ill [42]. Another study investigated increased anion gaps and their clinical significance and concluded that the increment in anion gap is related to an increased severity of illness that is independent of severe electrolyte abnormalities [43]. In this study, hospitalized patients who survived at least one week showed low risk of mortality.

The TCO_2 test often is conducted as part of the BMP. The process of metabolism produces carbon dioxide in our blood. Both high and low levels of TCO_2 in the blood may impact different systems related to cardiovascular functioning or cellular-based respiration. These changes may suggest the retention or loss of fluids, which may cause an imbalance in the body's electrolytes [44]. If a patient presents low levels of carbon dioxide, then less oxygen will reach the cells and tissues. On the other hand, if a patient presents high levels of carbon dioxide,

it may suggest a lung disease or infection. TCO_2 is correlated with the anion gap and is commonly measure for the diagnosis of metabolic acidosis, when the value falls below the lower "normal" limit of 23 mEq/L. Additionally, "*metabolic acidosis has been recognized as an important comorbid event in the high mortality rates seen in patients with end-stage renal disease*" [10].

To summarize, this chapter reviewed different parameters that have been used as biomarkers and that have been demonstrated, through several studies, to provide prognostic information. Also reviewed were different techniques or practices used for patient monitoring. Some of the most relevant studies reviewed were related to platelet count and its impact in patient monitoring processes and its correlation to patient outcome, including morbidity and mortality.

It is important to note that the level of platelets in blood depends on several processes (platelet production, maturation, sequestration, and destruction). All of these processes are affected by different factors, from the individual patient's characteristics and condition to drugs and treatments. Identifying changes in platelet count over time may provide new information about the underlying "systems" and a new understanding of the disease processes themselves. Similarly, modeling changes in some component elements of the BMP will support identifying changes in underlying "systems" that are elements of basic disease responses. In the following chapter, the methodology developed to analyze the parameters previously mentioned and reviewed in this chapter are described.

CHAPTER 3: METHODOLOGY

This chapter presents the methodology developed to achieve the goals of this study. First, the two different patient populations selected are described, and the reference event is defined for each dataset. Second, the study protocol is presented, which describes the metrics developed and presents the independent analysis of platelet count changes in each dataset. A key factor in the methodology is the process of synchronizing patient care cycles so that the changes of the parameters over time can be captured and compared. Third, a comparison of the results from both datasets is presented. Finally, the statistics applied to assess the metrics and the classification models and to compare the datasets are described. Considering specific objectives (1) and (2) the sequence to achieve them is the following: (i) selection of patient population, including determination of primary events, (ii) analysis of VA dataset, including definition of time frame (specific times intervals) and analysis of both metrics—rate of change and ratios in previously-defined time intervals, (iii) repetition of methodology applied to platelet count with MIMIC II dataset and (iv) graphical and statistical comparison of both datasets.

Objectives (3) and (4) of this research are related to broadening the scope to other parameters. To achieve them, the following activities will need to be conducted: (i) application and verification of methodology to other physiologic parameters using the homogeneous dataset, including individual analysis of each parameter, (ii) validation of methodology to simultaneously analyze homogeneous population and (iii) individual and simultaneous analysis of additional parameters from MIMIC II dataset.

Figure 3.1 presents a diagram of the methodology description, including the specific research objectives and the sequence of activities to achieve them.

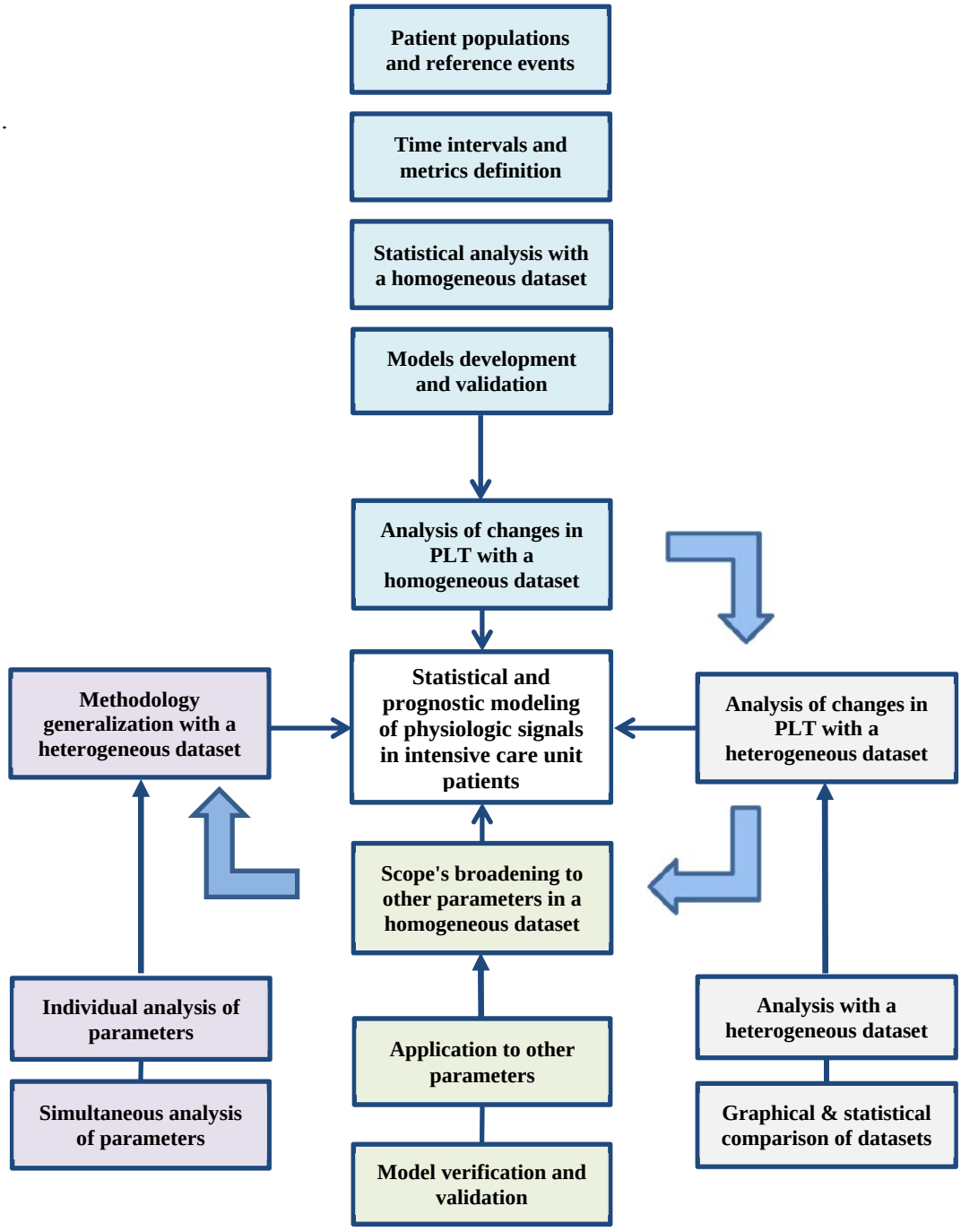


Figure 3.1. Methodology description

3.1 Patient Population's Selection

Two databases were used. The first database was composed of patients undergoing cardiac surgery at the James A. Haley Veterans Hospital (VA) in Tampa, Florida. The main focus was to analyze the behavior of changes in platelet counts over time using a more homogenous population. The second database was the MIMIC II clinical database (version 3), which is a component of the PhysioBank Archives**,** developed at the Massachusetts Institute of Technology (MIT) and at Boston's Beth Israel Hospital [44]. A heterogeneous sample of ICU patients was selected with different conditions and several hospital admissions. The purpose of using this database was to determine if the methodology could be generalized to a more heterogeneous population.

The first database contained 406 patients who underwent cardiovascular surgery (coronary artery bypass, aortic valve replacement, and mitral valve replacement) at the VA for a period of 3 years. The date and time of surgery were selected as the reference time. All platelet count values were assigned a relative time (in hours) from the reference time.

The second database contained records of more than 30,000 patients from a period of 7 years. All patients with platelet count values recorded were selected. The sample contained 1,308 de-identified ICU patients. More than a single admission was considered for survivors, but only last admissions were considered for non-survivors. As a result, 1,999 cases (a combination of patients and hospital admissions) were included for analysis. The original dataset included 15 percent of the population whose specific ICU admission time and date were unknown, 56 percent whose platelet count tests were taken after ICU admission, and 29 percent whose tests were taken before ICU admission. Considering the heterogeneity of the sample and that the exact ICU admission time was not available for all patients, the minimum platelet count value during the

first 24 hours after the first registered measure was selected as reference event or starting point for further analysis. The initial analysis of the more homogeneous cardiac surgery dataset suggested that platelet counts fall promptly after an acute event, which formed the basis for selecting this time interval to "synchronize" the patients' care cycles. The relative time to this event was computed for each subsequent platelet count value.

3.2 Study Protocol

3.2.1 Analysis Using the Veterans Hospital Dataset

3.2.1.1 Definition of Time Intervals

The behavior of survivors and non-survivors was analyzed by defining two specific reference points: t_A as the average time corresponding to the minimum platelet count for survivors, and t_B as the average time corresponding to the minimum platelet count for non-survivors. An analysis period was defined based on the platelet count behavior for survivors and non-survivors. A maximum period of t_3 hours was selected based on the platelet count changes observed and on the literature review that supports a minimum time that could provide prognostic information. Time intervals relevant to the study were defined as $T_1 = [t_A, t_1]$, $T_2 = [t_A, t_2]$ and $T_3 = [t_A, t_3]$, where t_A is used as the starting point of analysis, and t_1, t_2, and t_3 were defined as the upper limits of the time intervals. Intervals longer than t_3 hours were considered to be too late in the care cycle to be prognostically useful. Three other intervals were defined: $T_4 = [t_B, t_1]$, $T_5 = [t_B, t_2]$, and $T_6 = [t_B, t_3]$, using t_B as the starting point.

3.2.1.2 VA Dataset Analysis with Rates of Change and Ratios

Rc_i was defined as the rate of change of platelet counts over intervals $T_i, \forall i = 1,2,3$. Mean rates of change for survivors and non-survivors over those intervals were computed. These ratios

were subsequently compared to a more comprehensive analysis of the slope, anticipating that the simpler calculation of the ratio of values at two time points would be more usable in a clinical environment. A similar procedure was conducted for T_4, T_5, and T_6. Using those intervals, rates of change per hour $Rc_j, \forall j = 4,5,6$ were computed, and mean rates of change for survivors and non-survivors were calculated. Looking for a simple metric to analyze the platelets, three specific ratios were tested. We defined $r_i = \frac{PLT_i}{PLT_A}, \ \forall i = 1,2,3$ where PLT_i represents the platelet value measured at time t_i and PLT_A represents the platelet value measured at t_A.

Since measures were taken at different time intervals, a 10-hour interval was used to search values at the points t_i previously defined—i.e., the nearest measure to t_i was searched inside the interval $[t_i - 10, t_i], \forall i = 1,2,3$. Ratios r_i were computed for all patients and mean ratios were calculated.

A similar procedure was conducted using t_B as the starting point. Using the intervals $T_4, T_{5,}, T_6$, r_j was computed as $r_j = \frac{PLT_{j-3}}{PLT_B},, \forall j = 4,5,6$ where PLT_B represents the platelet value measured at t_B.

3.2.2 Analysis Using the MIMIC II Dataset

The primary event or starting point for each patient was defined as the time t_0 for the minimum platelet value during the first 24 hours after the first measure registered. All platelet values registered after t_0 were considered, and all corresponding time values were calculated with respect to time t_0. The methodology applied for the first dataset was repeated with the second dataset using the previously-defined relative times and platelet values.

3.2.2.1 MIMIC II Dataset Analysis with Rates of Change and Ratios

To construct the intervals $T_i, \forall i = 1,...,6$, times t_A, t_B, t_1, t_2 and t_3 were defined as relative times with respect to t_0. Using the platelet values recorded during the intervals $T_i, \forall i = 1,...,6$, rates of change per hour (Rc) were computed over each interval. Then, mean rates of change for survivors and non-survivors over the defined intervals were computed. The same procedure was followed using the second dataset; mean ratios were calculated using the same time intervals differentiating survivors and non-survivors.

3.3 Analysis and Comparison of the Datasets

Both datasets were analyzed individually to assess if the defined metrics could differentiate survivors from non-survivors. Then, both datasets were compared. The analysis was conducted graphically and statistically, comparing rates of change and ratios over each time interval. The objective was to analyze if the results from both datasets were comparable and if the methodology could be extended to a heterogeneous dataset. A critical assumption was that the values selected as first value and minimum value of the ICU patients from the MIMIC II dataset were realistic surrogates for the time of an actual acute event, because all the relative times computed were measured considering the time of this first registry as reference or time 0.

3.4 Multivariate Analysis

3.4.1 VA Multivariate Analysis

To evaluate if the methodology could be applied to other parameters, other physiologic parameters from the VA population were analyzed. The parameters available from this dataset were calcium, albumin, ionized calcium, and mean platelet volume (MPV). Calcium as a

biomarker and predictor of patient outcome was reviewed in the previous chapter. Ionized calcium (also called free calcium) is the calcium not attached to any protein in blood and helps in the building of bones and teeth. The behavior of this parameter was previously analyzed as a biomarker of patient outcome in cardiac surgery patients [40]. Mean platelet volume is another characteristic of platelets and may provide information on the speed of platelet production and release in the blood stream. It may be combined with platelet count to obtain a surrogate of platelet mass. Mean platelet volume is a surrogate for platelet age and, combined with platelet count, allows the estimation of the platelet mass, as shown in equation (1).

$$PLTmass = PLT \times MPV \tag{1}$$

With these platelet mass estimates, both metrics (ratios and rates of change) were calculated and assessed. Finally, the ratios and rates of change from all the parameters measured in the dataset were independently calculated and analyzed, and several parameters were analyzed simultaneously. To better observe the relationship between parameters, contour plots and surface plots were presented. The results of all the models created were compared with the results achieved with the platelet count values for the same group of patients.

3.4.2 MIMIC II Multivariate Analysis

The same methodology was applied with other parameters from the MIMIC II dataset. The parameters under study were albumin, calcium, anion gap, and total carbon dioxide. The characteristics of those parameters and their impacts on patient outcomes, including mortality and morbidity, were reviewed in the previous chapter. Of note is that unlike the VA dataset, where the parameter values were taken at the same time and from a specific group of cardiac patients (406 cardiac surgery patients), in the MIMIC II dataset, the different parameters to be analyzed were taken at different times and may come from a different set of patients from the

population (30,000 patients with diverse diseases). In this study, all cases registered for each parameter were considered, independent of the patient. Finally, several models were assessed to evaluate if their prediction power could be improved. In those models, the samples were per admission and not per patient.

3.5 Statistics

Fundamental basic descriptive statistics (mean and standard deviation) were used to evaluate the results. Two sample t-tests were conducted to evaluate differences in mean rates of change and mean ratios between survivors and non-survivors and also to evaluate differences between both datasets. Precision was given by one standard deviation (SD), and 95% confidence intervals (CI) were calculated for the means and medians. Medians were used in the cases of non-symmetric distributions.

Binary logistic regression models were developed using both metrics. The analysis of maximum likelihood estimates and likelihood ratios (LR) to evaluate the models were conducted using χ^2 test. Odds ratios (ORs) and corresponding 95% Wald confidence intervals for the selected factors were calculated and used for the analysis. The odds ratio was calculated by dividing the probability of non-surviving by the probability of surviving. The c-statistic was used to evaluate the performance of the logistic regression models and to compare the study results with previous studies. This statistic represents the area under the receiver operating characteristic (ROC) curve and was used to assess the discriminative power of the metrics.

Additionally, sensitivity analysis using bootstrapping was conducted to analyze the uncertainty of the parameter estimates, and 95% CI for those estimates were calculated. Ten-fold cross validation was used for the classification models; analysis of variance (ANOVA) was used

to evaluate the selected regression model; mean square error (MSE) and the predicted residual sum of squares statistic (CV press) were used to assess the models with both metrics over different intervals and compare them. Statistical significance was accepted at p-value ≤ 0.05. Data were managed using scripts in Matlab R2012a and analyzed using Minitab 16 and SAS 9.3.

CHAPTER 4: RESULTS AND DISCUSSION

This chapter presents the results and a discussion comparing these results with the results of previous studies. First, the behavior of platelet counts with the population from the VA dataset was reviewed, and then the behavior of the same parameter from the heterogeneous population was analyzed. The means for the defined metrics were compared graphically and statistically, including rates of change and ratios for specific time intervals in both datasets. Second, other parameters from the VA dataset were analyzed simultaneously. Third; other parameters from the MIMIC II dataset were also analyzed, individually and simultaneously. The last part of the chapter presents a discussion of the results and their impact in the patient monitoring process.

4.1 Results

The results shown below follow the sequence mentioned in the methodology section. In that section, two populations were described: a dataset from the VA and the MIMIC II dataset. In both datasets, the specific reference or acute events were defined. All the time values corresponding to each parameter value were relative times measured with respect to the time of the defined reference event. First, the results from the VA dataset were reviewed by applying the methodology to all the defined time intervals and then, the results from the MIMIC II dataset were reviewed. Then, both datasets were compared graphically and statistically. The next step was to repeat the methodology with other parameters from the VA dataset. Finally, other parameters from the MIMIC III dataset were reviewed by applying the methodology to specific

time intervals. Some observations from the graphs and comments are included after each result, and the final comments and conclusions are presented in Section 4.2.

4.1.1 VA Dataset

A total of 406 patients were analyzed from the VA dataset, which included 365 survivors and 41 non-survivors. Figure 4.1 shows the behavior over time of the platelet count for a sample of 56 patients, (survivors and non-survivors) during the first 300 hours after surgery. As can be seen, a drop occurred during the first 100 hours after surgery and then a rise of the platelets occurred, a fact that is more notable in survivors than non-survivors. During the interval of 300 hours, platelets for survivors continued to rise, while for non-survivors they did not. Nevertheless, in both cases, minimum values were observed during the first 100 hours.

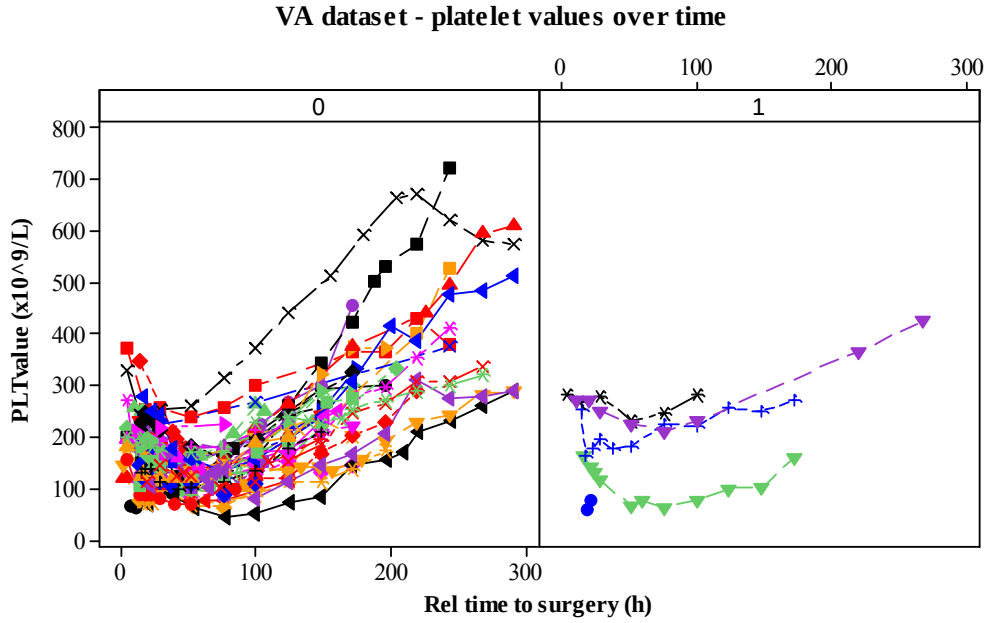


Figure 4.1. Platelet count over time - VA dataset

The time for the minimum platelet value after surgery for each patient was registered. The mean time for that minimum value was 53.4 ± 28.31 hours (95% CI = [51.9,54.8]) and 77.05 ± 59.69 hours (95% CI = [67.7,86.4]) for survivors and non-survivors, respectively. Observing the high variability, 95% CI for the median were calculated. The confidence intervals computed were [52,52] hours and [52,76] hours for survivors and non-survivors, respectively. Considering mean and median values from the previous results, t_A (average time corresponding to minimum platelet count for survivors) and t_B (average time corresponding to minimum platelet count for non-survivors) were set to 50 and 75, respectively. These times allowed the definition of the lower limits for the time intervals to be analyzed with the proposed metrics of rates of change and ratios.

It is important to note that the mean minimum platelet value for this population was 125.2 $\pm$ 47.58 x10^9/L for survivors and 139.9 ± 85.63 x10^9/L for non-survivors. However, median values were more representative, with 95% CI of [120.31,130.31] x10^9/L for survivors and [84.28,174.72] x10^9/L for non-survivors. Through both confidence intervals from the mean and the median, the variability in non-survivors was almost two times the variability presented in survivors for the minimum platelet value. However, in all cases, minimum platelet values were, on average, less than 150 x 10^9 /L, the "normal" reference range [23]. This issue confirms the statement that thrombocytopenia is commonly present in critically-ill patients such as this group of cardiac patients.

Observing the general behavior of platelet count (see Figure 4.1), a drop below 150x10^9/L occurred for the majority of the patients, and then the platelet count normalized or rose above this value during the first 200 hours. This fact agrees with the findings of prior authors, who found a clear decrease in platelet count during the first days in ICU [33, 46, 47]. A

similar situation was observed by Akca *et al.* [35], where platelet counts decreased in the first three days to reach a low point on day 4 for both survivors and non-survivors. It was established, then, that $t_3 = 200$ hours, and the study focused on intervals within this time frame.

Time intervals were defined as $T_1 = [50,100], T_2 = [50,150]$ and $T_3 = [50,200]$ for the first set and $T_4 = [75,100]$, $T_5 = [75,150]$ and $T_6 = [75,200]$ for the second set. Using these time intervals, the behavior of the rates of change and the behavior of the ratios were analyzed. Table 4.1 shows the basic descriptive statistics for the mean rates of change in survivors and in non-survivors. As shown, there was an increment in the mean rate of change for all intervals from T_1 to T_6 in both survivors and non-survivors. Nevertheless, if only one of the intervals is observed, there is also a clear difference between mean rates of change in survivors and non-survivors, with the mean rate of change for survivors being more than two times the rate of change of non-survivors. Another result is that the variability increased when the intervals T_4, T_5, T_6 were used, which means that the rate of change varied more when analyzing intervals beginning 75 hours after surgery.

Table 4.1. VA rates of change Rc_i, Rc_j - Descriptive statistics. S, survivors and NS, non-survivors

Rc_i	Rc_1		Rc_2		Rc_3	
	S	NS	S	NS	S	NS
Sample size	339	33	343	34	343	36
Mean (x10^9/L/h)	0.672	0.238	1.035	0.430	1.153	0.541
Standard Deviation	0.695	0.830	0.662	0.664	0.662	0.599
Rc_j	Rc_4		Rc_5		Rc_6	
	S	NS	S	NS	S	NS
Sample size	293	28	323	30	326	32
Mean (x10^9/L/h)	1.211	0.358	1.452	0.579	1.516	0.654
Standard Deviation	1.066	0.933	1.564	0.716	1.533	0.653

Figure 4.2 shows the typical behavior of platelet counts along interval T_3 (between approximately day 2 and day 8 after surgery). A difference in slopes between survivors and non-survivors can be observed. In this example, survivors presented a higher rise in platelet counts

than non-survivors. Moreover, most of the non-survivors maintained platelet count values of less than $100x10^9$/L, which categorized them as thrombocytopenic patients [35], confirming the results from previous studies that found associations between thrombocytopenia and mortality [27,29]. In this figure, it also can be observed that the platelet count decreased for a couple of patients; however, although the platelet value stabilized around $200x10^9$/L, which is considered a normal value, the patients did not survive. This may be an example of situations where a disorder in the platelet function is present or an adverse event occurred due to an unexpected factor. As defined previously, ratios r_i and r_j were used to estimate the slope with two points, the interval limits. To find the platelet values at 50, 100, 150, and 200 hours, the following intervals were defined: [40,50], [90,100], [140,150] and [190,200], respectively. The nearest value to the upper interval limit was used to determine the platelet value for calculating the corresponding ratio.

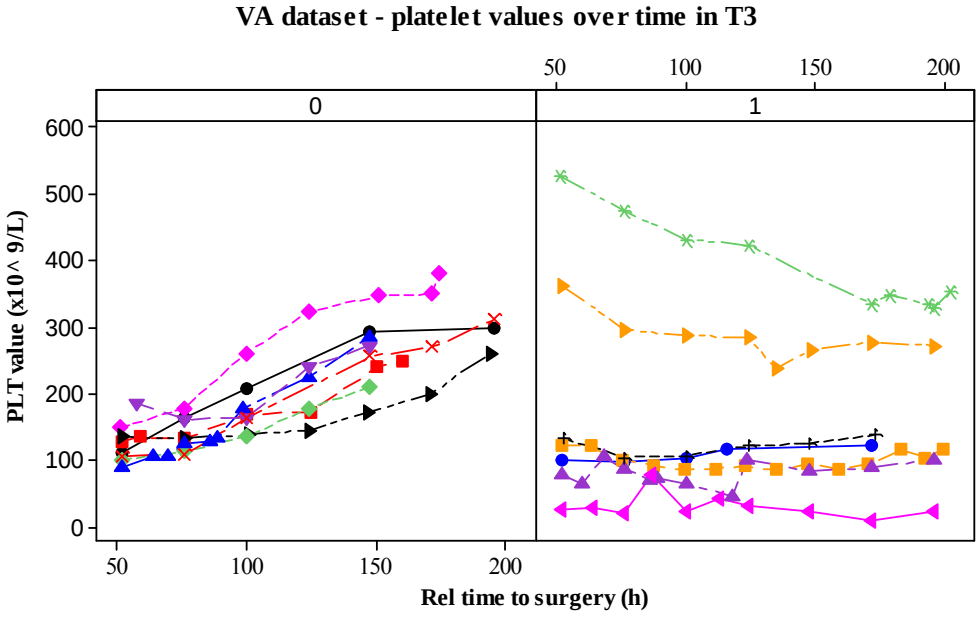


Figure 4.2. Platelet count over time in T_3 -VA dataset

Table 4.2 shows that the mean ratios and its variability increased according to the time interval length. All mean ratios calculated for survivors were greater than the mean ratios for non-survivors, confirming that the platelet counts rose more quickly in the former than in the latter.

Table 4.2. VA ratios r_i , r_j - Descriptive statistics. S, survivors and NS, non-survivors

r_i	r_1		r_2		r_3	
	S	NS	S	NS	S	NS
Sample size	254	28	169	21	112	19
Mean	1.280	1.098	1.809	1.324	2.395	1.573
Standard Deviation	0.285	0.252	0.545	0.452	0.960	0.754
r_j	r_4		r_5		r_6	
	S	NS	S	NS	S	NS
Sample size	271	27	185	22	119	19
Mean	1.221	1.099	1.787	1.324	2.398	1.571
Standard Deviation	0.203	0.194	0.591	0.324	1.110	0.819

To assess the results shown and evaluate if both metrics (rates of change and ratios) can differentiate survivors from non-survivors, two sample t-tests for the differences in mean were conducted. Of note is that the sample sizes for rates of change ($321 \le N \le 379$) were larger than the sample sizes for ratios ($131 \le N \le 298$). However, the proportion in percentage of non-survivors with respect to survivors was larger in ratios (between 10 and 17%) than in rates of change (between 9 and 10%). The tests showed that the mean rates of change from survivors and non-survivors were statistically different (p-value = 0.0060 for T_1 and p-values < 0.00001 for all other intervals). The same result was obtained for the mean ratios (p-value = 0.001 for T_1 and p-values < 0.00001 for all other intervals).

4.1.2 MIMIC II Dataset

This dataset was composed of 1,308 ICU patients with 1,999 admission cases and 23,665 platelet count measures. The time for the minimum platelet value after the reference time was registered. The mean time was 96 ± 146 hours for survivors and 144.7 ± 199.8 hours for non-

survivors. The median values were more representative, with 95% CI of [48.0, 51.3] and [60.3, 84.9] hours for survivors and non-survivors, respectively. As can be observed, the reference times set at $t_A = 50$ and $t_B = 75$ could be also used for this dataset, so that a comparison between both could be conducted.

Figure 4.3 shows the behavior of the platelet count for 30 cases, where the rate of change from survivors is higher than the rate of change from non-survivors. The difference in platelet count between survivors and non-survivors were not as notorious as the difference showed by the VA population from Section 4.1.1. However, it can be observed that platelet values for survivors reach normal values ($150x10^9$/L) between 200 and 300 hours, while for non-survivors the platelets maintain values less than the normal values.

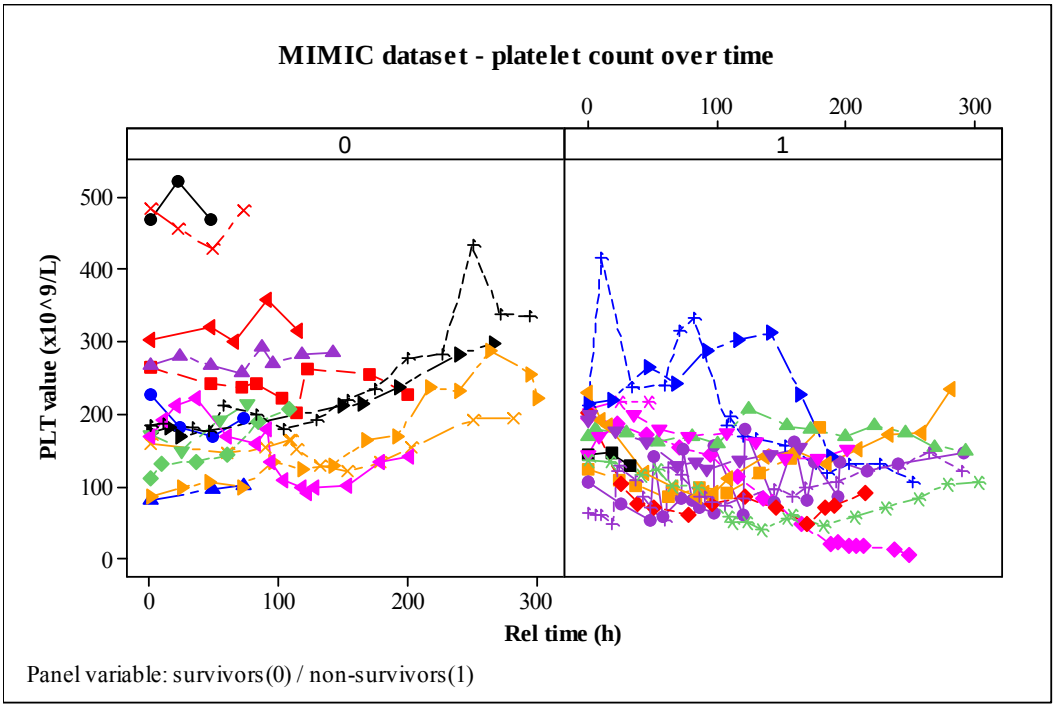


Figure 4.3. Platelet count over time - MIMIC II dataset

The mean minimum platelet value was $178.2 \pm 98.5 \text{x} 10^9$/L for survivors and $137.4 \pm 94.8 \text{x} 10^9$/L for non-survivors. Nevertheless, median values were more representative, with 95% CI of [157.0, 166.0] for survivors and [105.1, 133.8] $\text{x} 10^9$/L for non-survivors, respectively.

Table 4.3 shows an increment in the mean rate of change for all intervals T_1 to T_6 for survivors and non-survivors. However, observing each one of them, there was also a difference between mean rates of change from survivors and non-survivors. As observed in the VA dataset, the variability increases for intervals T_4, T_5 and T_6. The greatest difference in the mean rate of change was shown for T_3 ($0.50 \text{x} 10^9$/L/h), and in T_2 the mean rate of change of survivors was 18.2 times the mean rate for non-survivors.

Table 4.3. MIMIC II rates of change Rc_i, Rc_j - Descriptive statistics. S, survivors and NS, non-survivors

Rc_i	Rc_1		Rc_2		Rc_3	
	S	NS	S	NS	S	NS
Sample size	1012	235	1100	240	1122	240
Mean ($\text{x} 10^9$/L/h)	0.284	-0.024	0.473	-0.020	0.565	0.062
Standard Deviation	2.519	2.98	1.170	1.470	1.084	1.400
Rc_j	Rc_4		Rc_5		Rc_6	
	S	NS	S	NS	S	NS
Sample size	268	75	935	218	974	222
Mean ($\text{x} 10^9$/L/h)	0.078	-0.14	0.507	0.070	0.575	0.133
Standard Deviation	5.107	4.934	2.405	1.800	2.290	1.680

Using the same ratios defined for the VA dataset for all intervals T_1 to T_6, the results for r_i and r_j are shown in Table 4.4. As shown in Table 4.3 for the rates of change, the mean ratios increased according to the time interval length, and the mean ratios for survivors were greater than the mean ratios for non-survivors in almost all cases. Only in the case of the interval T_4 the mean ratio for survivors was less than the mean ratio for non-survivors.

Table 4.4. MIMIC II ratios r_i , r_j - Descriptive statistics. S, survivors and NS, non-survivors

r_i	r_1		r_2		r_3	
	S	NS	S	NS	S	NS
Sample size	468	117	336	90	238	68
Mean	1.074	0.975	1.291	1.048	1.522	1.186
Standard Deviation	0.282	0.594	0.557	0.455	0.948	0.675
r_j	r_4		r_5		r_6	
	S	NS	S	NS	S	NS
Sample size	486	122	344	96	244	75
Mean	1.059	1.094	1.271	1.146	1.468	1.261
Standard Deviation	0.194	0.698	0.442	0.595	0.810	0.730

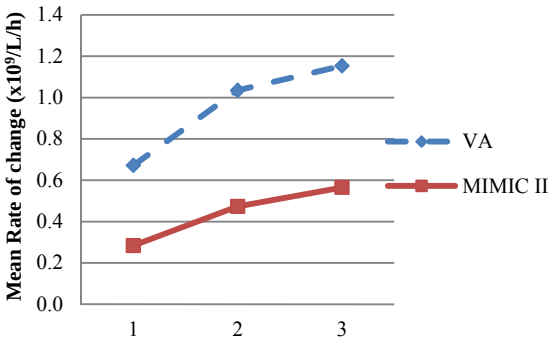
Table 4.4 shows that, unlike the sample sizes found for survivors and non-survivors derived by the computation of the metrics with the VA population, the sample sizes for rates of change ($363 \leq N \leq 1362$) were larger than the sample sizes for ratios ($306 \leq N \leq 608$), but not in all cases, and the proportion in percentage of non-survivors with respect to survivors were similar, between 25 and 30 percent for ratios and between 21 and 27 percent for rates of change. Two sample t-test showed that almost all mean rates of change from survivors and non-survivors were statistically different (p-value = 0.738 for T_1 and p-values < 0.003 for all other intervals). A similar result was obtained for the mean ratios (p-value = 0.595 for T_4, p-value = 0.057 for T_5 and p-values < 0.038 for all other intervals).

4.1.3 Comparison of the Datasets

To visualize the difference of both datasets in terms of the rate of change, cases 1, 2 and 3 were defined for the mean rate of change calculated for the intervals T_1, T_2 and T_3, respectively (See Table 4.1 and Table 4.3). Figures 4.4(a) and 4.4(b) show the mean rate of change for survivors and non-survivors, respectively. The dashed lines represent the trend of the VA dataset and the solid lines represent the trend of the MIMIC II dataset. In both figures, the trend is very similar. In both datasets, the mean rates of change increased as the interval length increased.

In general, it can be observed that the VA population had higher mean rates of change than the population from the MIMIC II dataset. The differences in mean rate of change were between 0.44 and 0.58 x10^9/L/h for survivors and between 0.45 and 0.53 x10^9/L/h for non-survivors. In both cases—survivors and non-survivors—the differences were very similar, an issue that can be observed in Figures 4.4(a) and 4.4 (b).

(a) Mean rate of change for survivors



(b) Mean rate of change for non-survivors

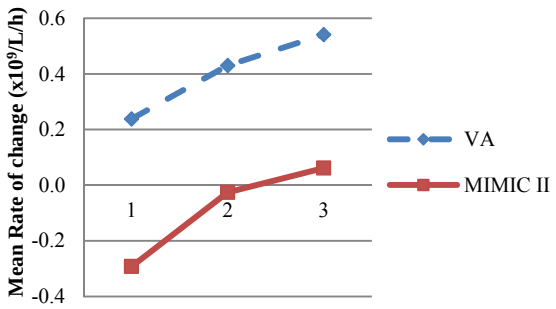
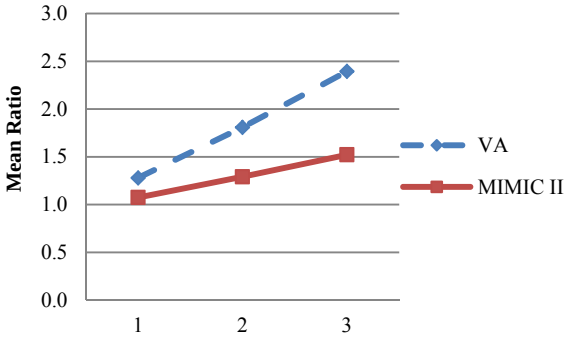


Figure 4.4. Mean rate of change for $T_1(1), T_{2,}(2), T_3(3)$, (a) survivors; (b) non-survivors

A similar situation is displayed in Figures 4.5(a) and 4.5(b) for the platelet count mean ratios. In this case, the mean ratios for T_1 were very similar in both datasets; however, after increasing the intervals (T_2 and T_3) the trend continued to be similar, but the means separated one from the other. The differences in mean ratio were between 0.20 and 0.87 for survivors and between 0.12 and 0.38 for non survivors. When using shorter time intervals, but starting at 75 hours after the first platelet count measure, similar trends were observed. Figures 4.6 and 4.7 show the corresponding cases 1, 2, and 3 for the mean rate of change and the ratios calculated for T_4, T_5 and T_6, respectively.

(a) Mean ratio for survivors



(b) Mean ratio for non-survivors

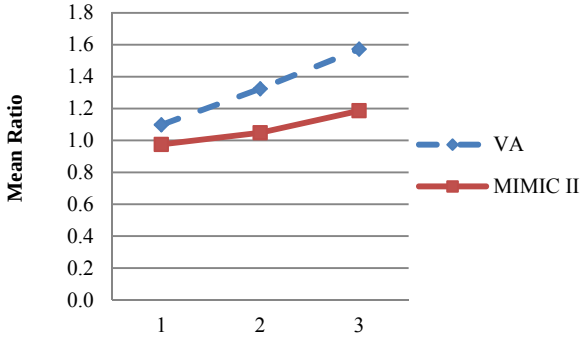
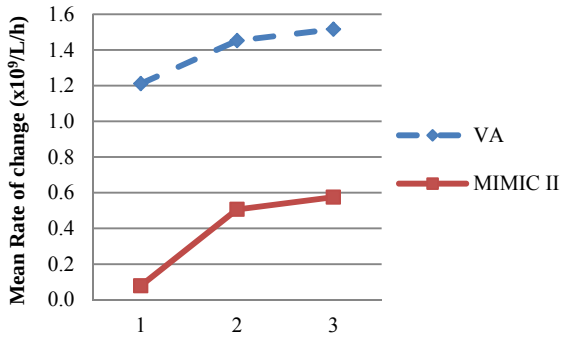


Figure 4.5. Mean ratio for $T_1(1), T_{2,}(2), T_3(3)$, (a) survivors; (b) non-survivors

(a) Mean rate of change for survivors



(b) Mean rate of change for non-survivors

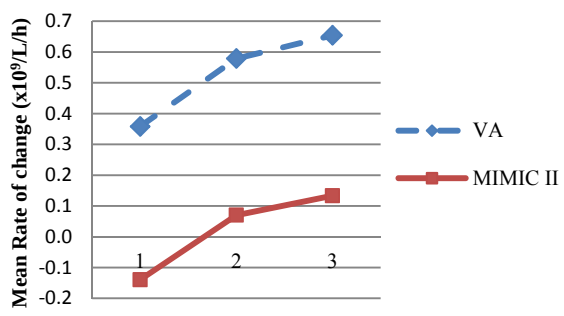
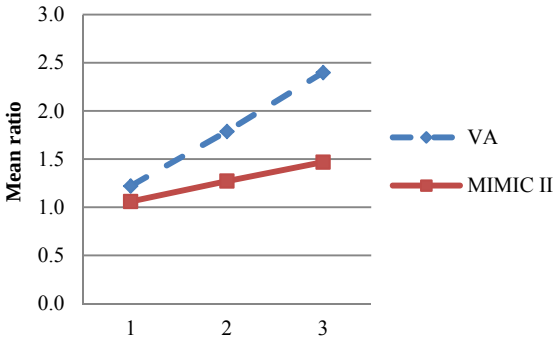


Figure 4.6. Mean rate of change for $T_4(1), T_{5,}(2), T_6(3)$, (a) survivors; (b) non-survivors

In Figures 4.6(a) and 4.6(b), the differences in mean rate of change were between 0.34 and 1.37 for survivors and between 0.50 and 0.83 for non survivors. In Figures 4.7(a) and 4.7(b), the mean ratios over T_4 for survivors and non-survivors are almost the same. The differences in mean ratios were between 0.16 and 0.93 for survivors and between 0.004 and 0.31 for non survivors.

(a) Mean ratio for survivors



(b) Mean ratio for non-survivors

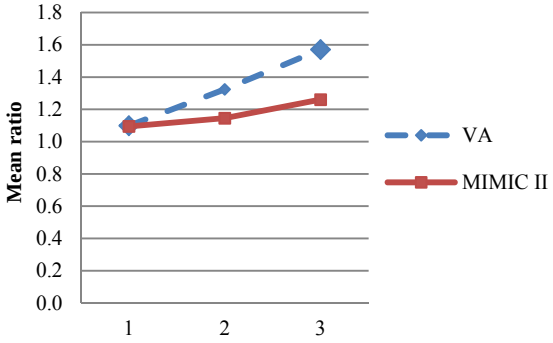


Figure 4.7. Mean ratio for $T_4(1), T_5,(2), T_6(3)$, (a) survivors; (b) non-survivors

Figures 4.4 to 4.7 show that both datasets display the same trend in the mean rate of change and the mean ratio. However, the greatest similarity is seen for the mean ratio in T_1 and T_4. In the following section a statistical comparison of the mean rates of change and mean ratios for survivors and non-survivors is presented.

4.1.3.1 Statistical Comparison of both Datasets

Considering that, graphically, the mean ratios for T_1 and T_4 for survivors and non-survivors were very similar in both datasets, two sample t-tests were conducted for the difference in mean ratios. The results were that T_1: p-value < 0.00001 for survivors and p-value=0.393 for non-survivors, and T_4: p-value < 0.00001 for survivors and p-value = 0.946 for non-survivors. Thus, it can be assumed that the mean ratios in T_1 and T_4 for non-survivors in both datasets are statistically the same. All differences between mean rates of change and mean ratios were tested statistically, and, in addition to the conclusions stated previously, the rates of change in T_1 (p-value=0.393) and T_4 (p-value=0.406) for non-survivors in both datasets also was demonstrated to be statistically the same. Additionally, the ratio in T_6 (p-value=0.145) also showed no statistical differences between their means.

4.1.3.2 Classification Models

Logistic regression models were constructed with all ratios and rates of change previously defined. Table 4.5 presents the parameter estimates, odds ratios, and corresponding 95% CI for those estimates together with c-statistics for the best models. It can be observed that the best models for the VA dataset had a c-statistic of 0.78 for rates of change and ratios in T_5 and T_6, whereas for the MIMIC II dataset, the maximum c-statistic was 0.64 with the model of platelet count ratios in T_2. The analysis of maximum likelihood estimates for the parameters and the likelihood ratio test for the models showed that all were significant (p-values<0.0001).

Table 4.5. Best logistic regression models. Rc_i, Rc_j, rates of change; r_i, r_j, ratios

			Intercept	x	Odds ratio		c-statistic
					Point estimate	95%CI	
VA dataset	Rc_i	Rc_2	-1.189	-1.534	0.22	[0.11,0.41]	0.74
		Rc_3	-0.880	-1.627	0.20	[0.10,0.38]	0.75
	r_i	r_2	1.327	-2.214	0.11	[0.03,0.37]	0.75
		r_3	1.317	-1.619	0.20	[0.08,0.50]	0.77
	Rc_j	Rc_5	-1.017	-1.408	0.25	[0.14,0.44]	0.78
		Rc_6	-0.701	-1.556	0.21	[0.11,0.39]	0.78
	r_j	r_5	2.118	-2.770	0.06	[0.02,0.24]	0.78
		r_6	1.185	-1.586	0.21	[0.08,0.51]	0.78
MIMIC II dataset	r_i	r_2	-0.033	-1.118	0.33	[0.18,0.59]	0.64
		r_3	-0.401	-0.644	0.53	[0.33,0.84]	0.63

Additionally, sensitivity analysis using bootstrapping with 100 replicates was conducted to observe the uncertainty of the parameter estimates. After repeating the sampling applying bootstrap, 95% CI for those estimates were calculated. All estimate values were inside the confidence intervals, suggesting the validity of the parameters. The results from this analysis are presented in Appendix A.

Ten-fold cross validation for all models was conducted. Table 4.6 shows the best models considering MSE and CV press for each dataset. It can be observed that the ratio and rate of change in T_2 showed a good result for the VA dataset with smaller MSE and CV press and also ratios in T_3 and T_4. However, for the MIMIC II dataset, the best models were obtained with the ratios in T_2 and T_3.

Table 4.6. Best models from 10-fold cross validation. Rc_i, Rc_j, rates of change; r_i, r_j, ratios; MSE, mean square error; CV press, predicted residual sum of squares statistic

			Intercept	x	CV press	MSE
VA dataset	Rc_i	Rc_2	0.194	-0.106	29.4	0.08
	r_i	r_2	0.383	-0.155	17.5	0.09
		r_3	0.390	-0.107	15.5	0.12
	r_j	r_4	0.384	-0.244	24.2	0.08
MIMIC II dataset	r_i	r_2	0.380	-0.136	69.3	0.16
		r_3	0.326	-0.071	52.3	0.17

Comparing the previous results from the two datasets, it can be concluded that metrics for intervals T_2 and T_3 showed the best results in terms of reduced MSE and CVpress. The next step was to repeat the methodology with other parameters from the VA dataset to evaluate the applicability of the methodology to other physiologic signals and then to evaluate if the inclusion of several parameters could enhance the predictive power of the models.

4.1.4 Other Physiologic Parameters from the VA Dataset

The parameters available from the VA dataset were calcium, albumin, ionized calcium, and mean platelet volume (MPV). All these parameter values were measured during the same time interval as the platelet count values. However, a sample of only 308 patients had registered values for those parameters. The number of albumin tests registered accounted for only 15 patients, and from them, only 8 ratios could be computed. Ionized calcium was registered for

only 13 patients, so this small sample was not taken into account. The final set of parameters to repeat the methodology was composed of mean platelet volume and calcium.

4.1.4.1 Mean Platelet Volume Analysis

A total of 308 patients from the VA dataset were analyzed, including 289 survivors and 19 non-survivors. This sample contained 7,758 MPV measures. The mean MPV was 8.38 ± 0.90 fL (95% CI = [8.36, 8.40]) and 8.25 ± 1.01 fL (95% CI = [8.18,8.31]) for survivors and non-survivors, respectively. Figure 4.8 shows the general behavior of the mean platelet volume over time.

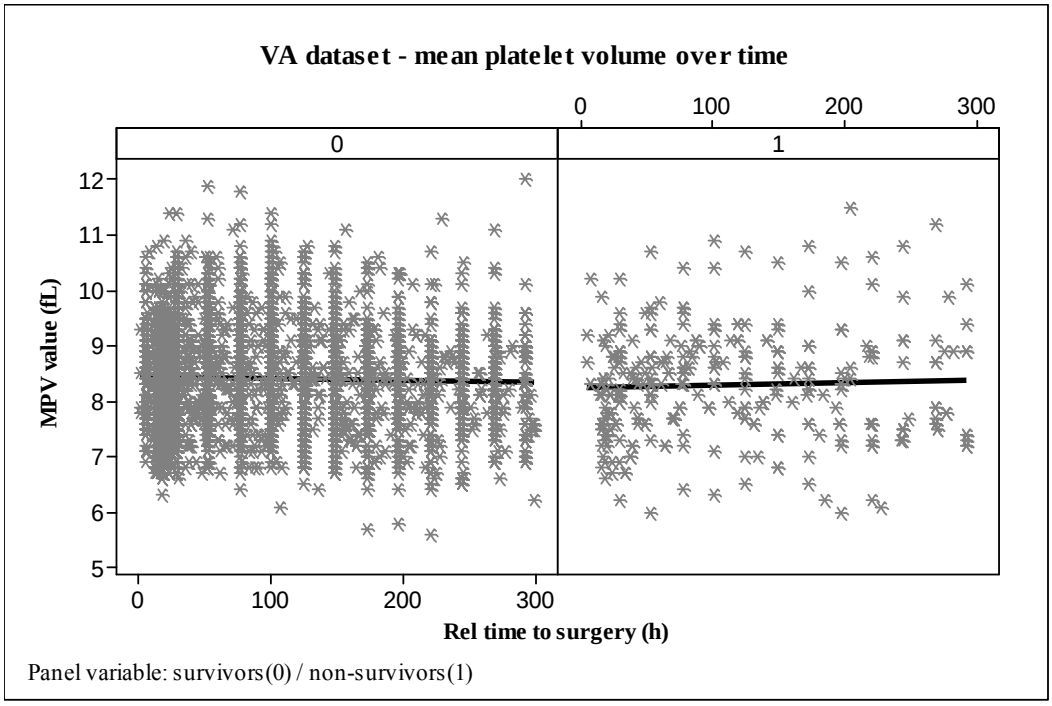


Figure 4.8. Mean platelet volume data over time - VA dataset

From Figure 4.8, the differences between survivors and non-survivors are not clear. Previous studies have concluded that high values of MPV are related with poor outcomes, but in specific diseases. For example, a study found that an increased MPV was independently related to a poor outcome in patients with acute ischemic cerebrovascular events [48], and another study

that analyzed platelet size in stroke patients [49] found that an increased MPV and a low levels in platelet count were features of both the acute and the non-acute phases of cerebral ischemia. Another study that analyzed increments in MPV in patients with chronic renal failure also concluded that " *larger platelets are more reactive and may contribute to an increased risk of thrombosis*" [50].

Table 4.7 shows the logistic regression models for rates of change and ratios in intervals T_2 and T_3. None of the models constructed for rates of change and ratios showed a significant c-statistic, confirming the results of mean values previously presented, which were very similar between survivors and non-survivors and the behavior of MPV displayed in Figure 4.8.

Table 4.7. MPV - Best logistic regression models for rates of change and ratios

			Intercept	x	Odds ratio		c-statistic
					Point estimate	95%CI	
VA dataset	Rc_i	Rc_2	-2.909	-23.420	0.0001	[<0.001,5.1860]	0.51
		Rc_3	-2.895	-9.620	0.0001	[<0.001,>999.9]	0.53
	r_i	r_2	-2.911	0.201	1.2220	[<0.001,>999.9]	0.44
		r_3	-2.419	-0.323	0.7240	[<0.001,>999.9]	0.51

Two sample t-tests were also conducted to statistically verify if the models can differentiate survivors from non-survivors. As a result, none of the models could make the differentiation (0.36<p-values<0.95). This result is supported by low c-statistics less than 0.53. Appendix A provides complete descriptive statistics and p-values for the differences in mean for both metrics, ratios and rates of change.

4.1.4.2 Calcium Analysis

A total of 308 patients from the VA dataset were analyzed, including 289 survivors and 19 non-survivors. This sample contained 8,047 calcium measures. The mean calcium value was 8.76 ± 0.79 mg/dL (95% CI = [8.74, 8.78]) and 8.64 ± 10.77 mg/dL (95% CI = [8.59,8.69]) for

survivors and non-survivors, respectively. Figure 4.9 shows the general behavior of the calcium data over time, where differences between survivors and non-survivors were notable. An increasing trend for survivors can be seen, whereas for non-survivors, the calcium values do not show any specific trend.

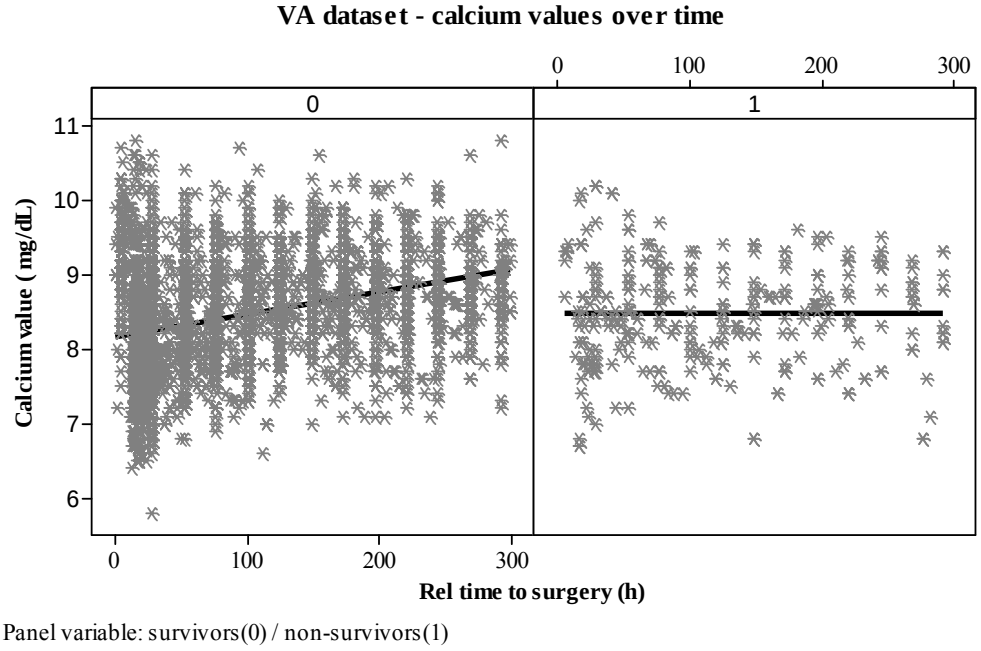


Figure 4.9. Calcium data over time - VA dataset

According to the National Institute of Health, the reference range for calcium is from 8.5 to 10.2 mg/dL [51]. As shown, most of the patients, both survivors and non-survivors, presented calcium values that were lower than the minimum normal level, even 300 hours (~12 days) after the date of the surgery. This issue provides signs of hypocalcemia, which is a common finding in critically-ill patients [52]. Nevertheless, it can also be observed that there are some patients with normal levels after 200 hours who did not survive. This situation could be due to possible post-surgical complications, which are not addressed in this research.

We need to consider that, although the VA dataset is composed of patients who underwent similar cardiac surgeries, each patient has a different condition and his/her organism reacts different to the intervention and treatment.

Table 4.8 shows the logistic regression models for the rates of change and ratios for intervals T_2 and T_3. The results for models constructed with rates of change were better ($0.79 \leq c \leq 0.80$) than the results for the models constructed with calcium ratios ($0.66 \leq c \leq 0.72$). This result is similar to the result observed for platelet count in this population, where rates of change performed better than ratios, but in shorter intervals starting up 75 hours (T_5 and T_6.) However, platelet count ratios performed equal to or better than the rates of change for the same intervals T_2 and T_3. Two sample t-tests showed that only rates of change for T_1 and T_2 could differentiate survivors from non-survivors; the other metrics could not (0.14< p-values<0.79). Appendix B provides complete descriptive statistics and p-values for the differences in mean for both metrics ratios and rates of change.

Table 4.8. Calcium - Best logistic regression models for rates of change and ratios

			Intercept	x	Odds ratio		c-statistic
					Point estimate	95%CI	
VA dataset	Rc_i	Rc_2	-2.592	-96.238	<0.001	[<0.001,<0.001]	0.80
		Rc_3	-2.554	-113.800	<0.001	[<0.001,<0.001]	0.79
	r_i	r_2	3.804	-6.181	0.0020	[<0.001,1.7170]	0.66
		r_3	6.888	-9.195	0.0001	[<0.001,1.3900]	0.72

Two sample t-tests showed that only rates of change for T_1 and T_2 could differentiate survivors from non-survivors; the other metrics could not (0.14< p-values<0.79). Appendix B provides complete descriptive statistics and p-values for the differences in mean for both metrics ratios and rates of change.

Considering that the ten-fold cross validation in Section 4.1.3.2 showed that ratios in T_2 and T_3 had the best results in both datasets, a preliminary analysis was conducted with r_2 **.** The physiologic parameters considered were platelet count, calcium, and mean platelet volume.

4.1.4.3 Preliminary Multivariate Analysis using r_2

The VA dataset with values for ratios r_2 for platelet counts, calcium, and mean platelet volume were used for the analysis. The sample was composed by 126 patients, including 8 non-survivors. To visualize the differences between survivors and non-survivors, surface plots are shown in Figure 4.10 and contour plots are shown in Figure 4.11.

The surface plots show that ratios of platelet count were higher for survivors than non-survivors. Figure 4.11 better demonstrates the differences in platelet count and calcium ratios for survivors and non-survivors. More survivors had higher ratios of platelet count that were more than 2 and calcium ratios that are more than 1, whereas the majority of non-survivors had platelet count ratios less than 1.6.

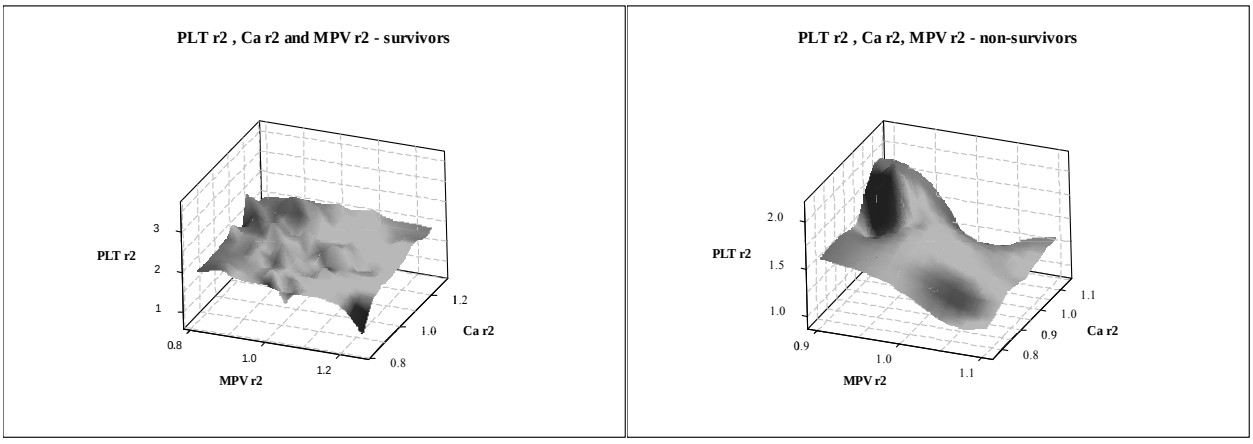


Figure 4.10. Surface plots of ratios in T_2 with PLT r_2 , Ca r_2 and MPV r_2

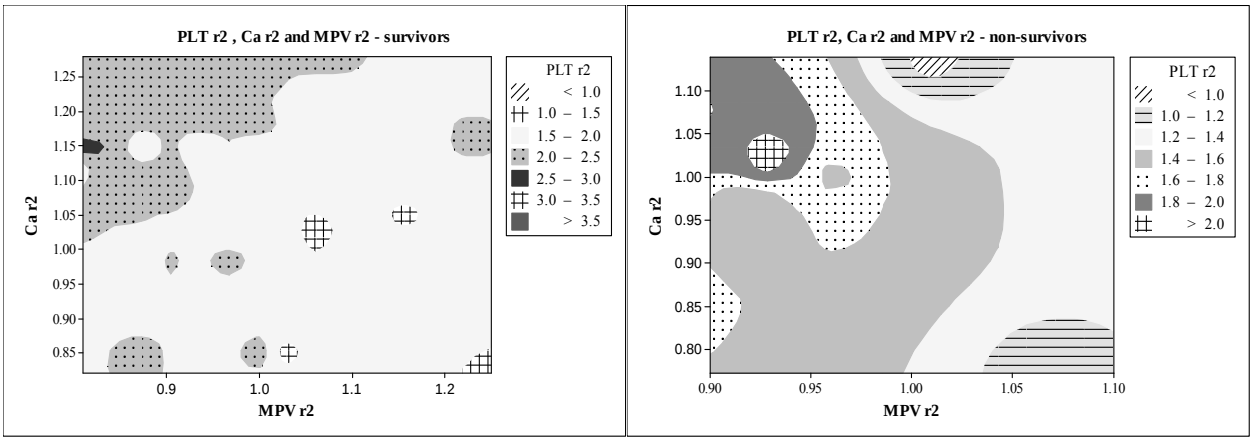


Figure 4.11. Contour plots of ratios in T_2 with PLT r_2, Ca r_2 and MPV r_2

Figure 4.11 shows that, in the plane formed by MPV and calcium ratios in T_2, the biggest region observed for survivors is given by ratios of platelet count that were between 1.5 and 2, whereas the biggest region for non-survivors is given by ratios of platelet count between 1.2 and 1.6.

Table 4.9 shows the logistic regression model for ratios in T_2: platelet count, calcium and MPV. The c-statistic for the model was 0.748, and the smaller odds ratio was for the calcium ratio.

Table 4.9. PLT, Ca and MPV ratios in T_2 - Best logistic regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	14.984	-	
PLT r_2	-1.6673	0.189	[<0.001, 0.910]
Ca r_2	-8.9479	<0.001	[<0.001,274.1]
MPV r_2	-5.7314	0.003	[0.026, 1.383]
c-statistic	**0.748**		

As presented in Section 3.4.1, the mean platelet volume was a surrogate for the platelet age and, combined with the platelet count, allows the estimation of platelet mass. Using the same VA dataset of 308 patients and equation (1) from Chapter 3, platelet mass was estimated. This

sample contained 6,927 platelet mass values. The mean platelet mass was $1842.9 \pm 892.5 \times 10^{-6}$ (95% CI = [1820.6,1865.1] $\times 10^{-6}$) and $1643.1 \pm 737.3 \times 10^{-6}$ (95% CI = [1599.5,1696.8]$\times 10^{-6}$) for survivors and non-survivors, respectively. Repeating the methodology previously described, the behavior of platelet mass is shown in in Figure 4.12.

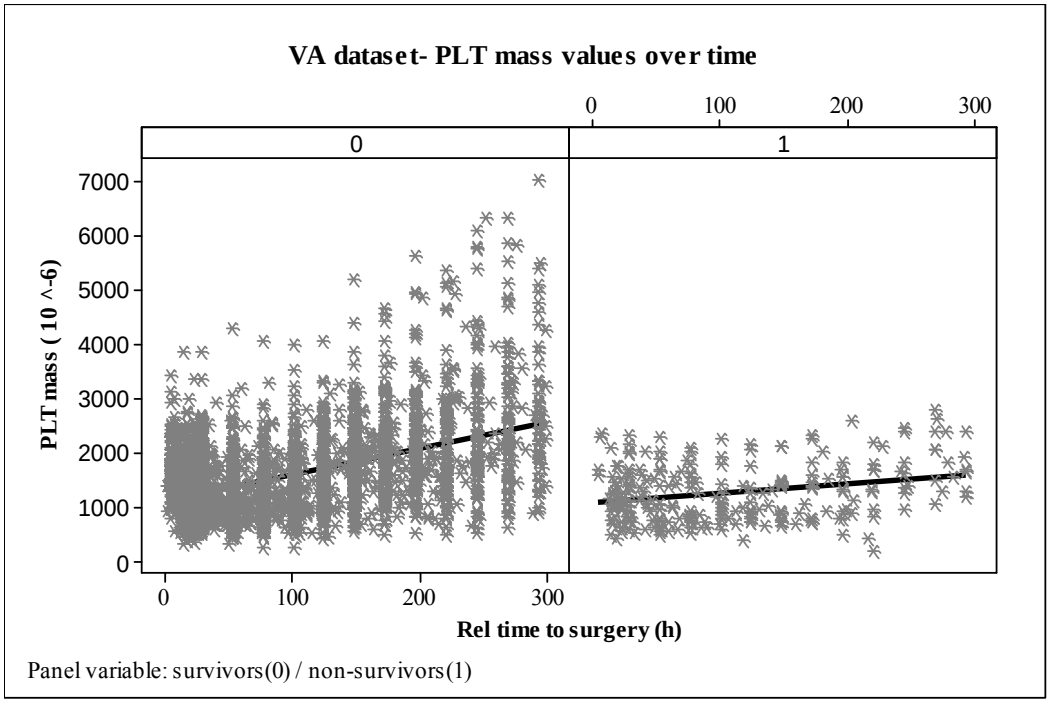


Figure 4.12. Platelet mass data over time - VA dataset

In this figure we can observe that the trends in survivors differ from the trends in non-survivors. As observed for the calcium and platelet count, the platelet mass showed an increasing trend for survivors. Ratios and rates of change were computed for platelet mass, and the best logistic regression models with this parameter for both metrics in T_2 and T_3 were constructed. Table 4.10 shows the estimates for the models; the best c-statistic (c=0.78) was calculated for the rate of change in T_3.

Table 4.10. PLT mass - Best logistic regression models. Rc_i, Rc_j, rates of change; r_i, r_j, ratios

			Intercept	x	Odds ratio		c-statistic
					Point estimate	95%CI	
VA dataset	Rc_i	Rc_2	-2.3882	-0.0872	0.91	[<0.001,<0.001]	0.77
		Rc_3	-2.0883	-0.1334	0.87	[<0.001,<0.001]	0.78
	r_i	r_2	-0.8533	-1.2052	0.30	[<0.001,1.7170]	0.69
		r_3	-1.0698	-0.9069	0.40	[<0.001,1.3900]	0.71

Two sample t-tests between mean rates of change and mean ratios showed that only the rates of change for T_1 and T_2 and the ratios for T_2 could differentiate survivors from non-survivors; the other metrics could not (0.098< p-values<0.20). Appendix A provides complete descriptive statistics and p-values for the differences in mean for both metrics, ratios and rates of change.

If these results are compared with the previous results obtained for platelet counts in terms of c-statistic, it can be concluded that the use of platelet mass improves the predictive power of the rate of change. The c-statistic for Rc_2 (rate of change in interval T_2) improved from 0.74 to 0.77 and for Rc_3 (rate of change in interval T_3) improved from 0.75 to 0.78. However, the c-statistic for the ratio r_2 decreased from 0.75 to 0.69 and for r_3 decreased from 0.77 to 0.71.

Considering the improvement of the results using platelet mass, compared to the results using platelet count values, a preliminary analysis combining calcium and platelet mass in T_2 was conducted. Figure 4.13 shows a scatter plot from rates of change of calcium and platelet mass. In this figure we can observe a trend of higher platelet values and higher calcium values (positive trend) for survivors. However, a clear decrement of those parameters (negative trend) is shown for non-survivors. This issue confirms that the recovery process is different in survivors and non-survivors.

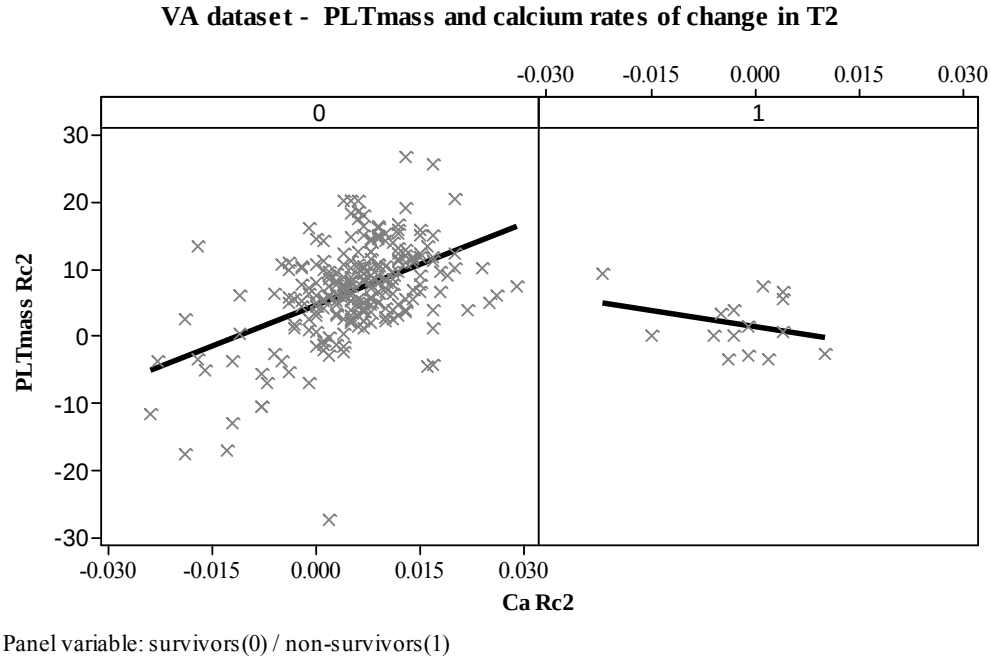


Figure 4.13. Platelet mass and calcium rates of change in T_2 - VA dataset

Table 4.11 shows the best logistic regression model for platelet mass and calcium rates of change. The predictive power of the model increased (c=0.834). However, the calcium parameter was more significant, with a very high estimate compared to the platelet mass.

Table 4.11. PLT mass and Ca rates of change in T_2 - Best logistic regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-2.448	-	
PLT mass Rc_2	-0.038	0.963	[0.892, 1.039]
Calcium Rc_2	-78.8	<0.001	[<0.001, <0.001]
c-statistic	**0.834**		

Since the ratios in T_2 showed better results for the MIMIC II dataset, this metric was also analyzed. Figure 4.14 shows the behavior of the ratios for T_2. It can be observed that the relationship between ratios for platelet mass and calcium in T_2 had a positive trend for survivors.

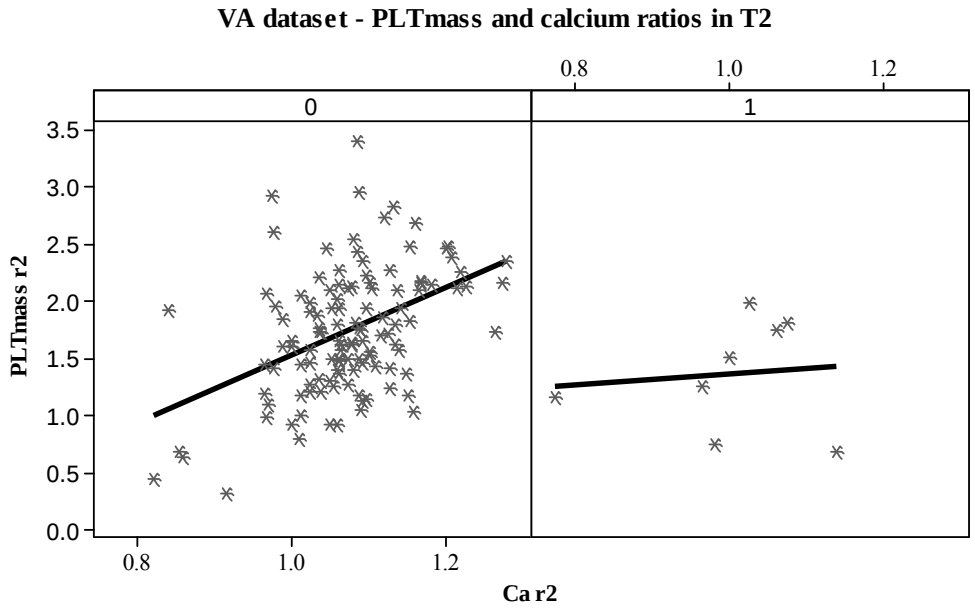


Figure 4.14. Platelet mass and calcium ratios in T_2 - VA dataset

Although an increasing trend is shown for survivor, for non-survivors, there was not a notable relationship. Of note is that the sample size for non-survivors was reduced to eight; the results for non-survivors are inconclusive. Table 4.12 shows the best regression model using platelet mass and calcium ratios. It can be observed that the platelet mass had a higher impact in the regression model, and the c-statistic was lower than the statistics for the rate of change using the same parameters. It can be concluded that the predictive power of the model decreases using ratios instead of rates of change, but since the objective was to extend the methodology to a broader population, the ratios were considered for the next step.

Table 4.12. PLT mass and Ca ratios in T_2 - Best logistic regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	5.40	-	
PLT mass r_2	-0.69	0.497	[0.103, 2.399]
Calcium r_2	-6.7	0.001	[<0.001, 8.282]
c-statistic	**0.754**		

At this point in the study, the multivariate analysis considered each parameter independently and how it directly affects the patient outcome. However, how the addition of interaction terms in the model could improve the results must be evaluated. Therefore, interaction terms were added in both models from Table 4.11 and Table 4.12. The results showed a slight improvement in the value of the c-statistic. In the case of the model for rates of change, the addition of an interaction term between platelet mass rate of change and calcium rate of change increased the c-statistic from 0.83 to 0.86. The analysis of maximum likelihood showed that the interaction term was significant (p-value=0.006). Similarly, in the case of the ratios, the interaction term improved the c-statistic from 0.75 to 0.77. However, in this case, the analysis of maximum likelihood showed that the interaction term was not significant (p-value=0.132). The complete regression model including all the terms and estimates is presented in Appendix C.

4.1.5 Analysis of Other Parameters from the MIMIC II Dataset

From the previous section, it was determined that calcium and platelet mass can provide prognostic information. The MIMIC II dataset contains information about different laboratory tests. However, the focus herein will continue to be on hemodynamic parameters. The methodology is repeated using the calcium tests from the MIMIC II dataset and other parameters. As defined previously, other parameters that could be included are albumin, anion gap, and total CO_2. In the case of platelet mass, the MIMIC II dataset does not contain information regarding mean platelet volume; thus, an estimation of platelet mass is not possible.

The behavior of calcium was analyzed so a comparison with the VA dataset could be conducted. Then, the methodology applied to albumin, total carbon dioxide, and anion gap was repeated. After analyzing each parameter independently, they were combined and the impact of those combinations was assessed.

4.1.5.1 Calcium Analysis – MIMIC II Dataset

A total of 1,650 patients from the MIMIC II dataset were analyzed, including 802 survivors and 848 non-survivors. Those patients had at least two measures registered during the period of analysis. This sample contains 1,660 admission cases and 11,781 measures. The mean calcium values were 8.37 ± 0.76 mg/dL (95% CI = [8.35, 8.39]) and 8.28 ± 0.78 mg/dL (95% CI = [8.27,8.30]) for survivors and non-survivors, respectively. It was observed that the mean values were very similar for both survivors and non-survivors. Nevertheless, the confidence intervals calculated for the means did not overlap; thus it can be concluded that, on average, survivors have higher mean calcium levels than non-survivors.

Figure 4.15 displays the general behavior of the calcium data over time for 30 admission cases (i.e. combination between ICU admission and patient).

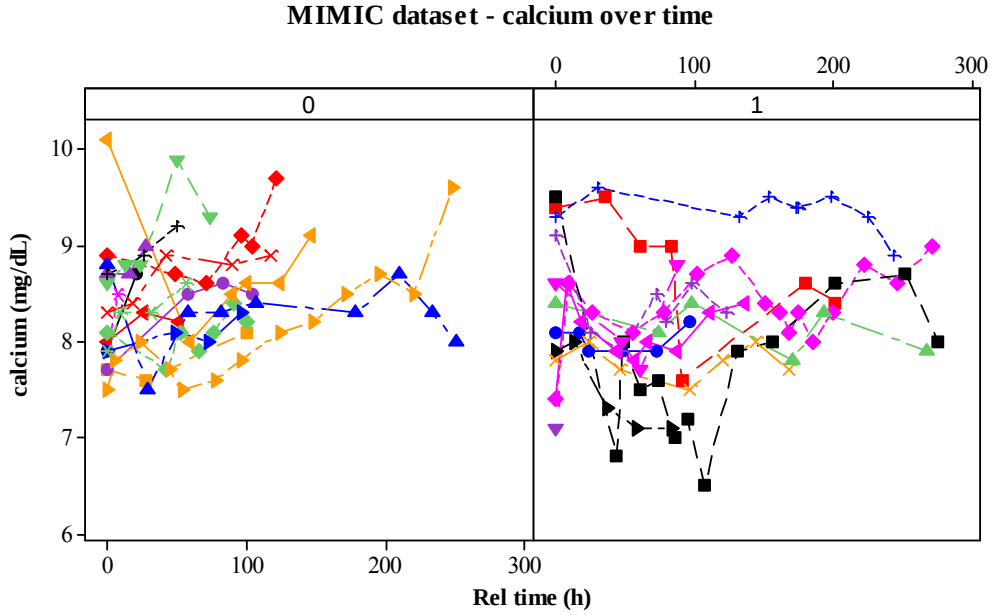


Figure 4.15. Calcium data over time - MIMIC II dataset

As seen for the calcium data from the VA dataset, the calcium levels for survivors and non-survivors decreased during the first 100 hours. Most of the calcium levels dropped below 8.5 mg/dL, the lower limit for a "normal" range [50], an issue that confirms that hypocalcemia is commonly presented in critically-ill patients [40].

Figure 4.15 shows that the drop in calcium level for survivors was not as abrupt as the drop for non-survivors and that the recovery of survivors could be seen during the first 150 hours after the reference event. However, the behavior of calcium levels in non-survivors did not show a specific pattern, since calcium levels in some cases were over the lower normal limit of 8.5 mg/dL [50].

Table 4.13 presents the logistic regression models for the calcium ratios and rates of change. The table shows that the results for calcium levels with the MIMIC II dataset varied from the results obtained with the VA dataset. The c-statistics for the models with the ratios and the rates of change, based on the MIMIC II dataset, were lower ($c \leq 0.60$) than the c-statistics for the models obtained using the VA dataset ($0.66 \leq c \leq 0.80$). All odds ratio estimates were higher than the estimates found for the VA dataset, where the odds ratio estimates were less than 0.001. However, as seen before for the platelet count in the intervals T_1 and T_2, the ratios provided better results than the rates of change.

Table 4.13. Logistic regression models for calcium. Rc_i, rates of change; r_i, ratios

			Intercept	x	Odds ratio		c-statistic
					Point estimate	95%CI	
MIMIC II dataset	Rc_i	Rc_1	0.3006	0.5557	1.743	[0.005,579.58]	0.47
		Rc_2	0.2151	1.0074	2.738	[0.120,62.305]	0.46
		Rc_3	0.1799	1.3587	3.891	[0.093,162.13]	0.45
	r_i	r_1	0.7082	-0.5204	0.594	[0.047,7.524]	0.53
		r_2	1.2476	-0.978	0.376	[0.032,4.358]	0.56
		r_3	2.3719	-2.0547	0.128	[0.007,2.361]	0.60

Two sample t-tests between mean rates of change of survivors and non-survivors, as well as between mean ratios, did not show statistical differences between means (0.148<p-values <0.85). This result suggests that both metrics based on calcium values could not differentiate survivors from non-survivors. It is important to note that, although no statistical differences could be found between survivors and non-survivors using these metrics, there is a clear difference in the recovery process of survivors and non-survivors, as shown in Figure 4.15. In this figure we observed that the calcium level for survivors recover very quickly during the first 150 hours after the reference event.

The next step was to analyze other parameters that have shown, through previous studies, to have any prognostic significance among ICU or critically-ill patients. As stated in Chapter 2, there are other physiologic parameters measured through blood tests (albumin, anion gap, and total carbon dioxide) that vary their behavior in patients with acute illnesses. Those parameters were analyzed individually and then together to determine if the hidden interaction between them can provide more information regarding the patient outcome.

4.1.5.2 Albumin Analysis – MIMIC II Dataset

A total of 676 patients from the MIMIC II dataset were analyzed, including 270 survivors and 406 non-survivors. This sample contained 680 admission cases and 2,305 measures. The mean albumin values were 2.94 ± 0.71 g/dL (95% CI = [2.90, 2.99]) and 2.64 ± 0.59 g/dL (95% CI = [2.61, 2.67]) for survivors and non-survivors, respectively. As seen for the mean calcium levels, the mean albumin levels show differences between survivors and non-survivors. It can be seen that the confidence intervals for the mean values did not overlap, and on average, albumin levels for non-survivors were lower than albumin levels for survivors. Figure 4.16 shows the general behavior of the albumin data over time for a sample of 30 admission cases.

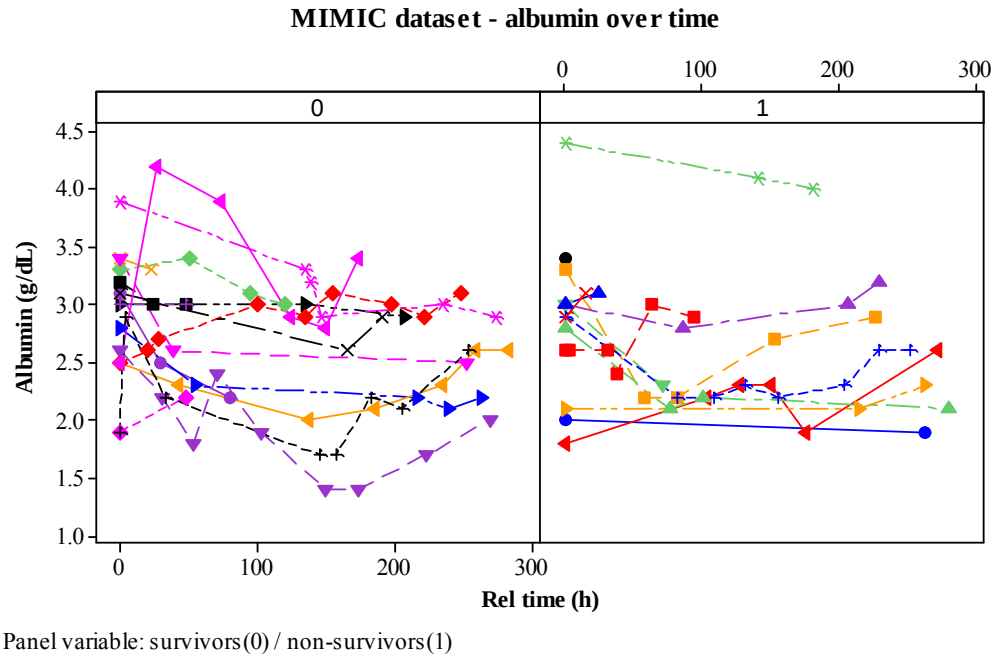


Figure 4.16. Albumin data over time - MIMIC II dataset

In the previous figure we cannot observe notable differences between survivors and non-survivors. Nevertheless, more variation in the albumin level was present for survivors. According to the National Institute of Health, the reference range for albumin is from 3.4 to 5.4 mg/dL [53]. In Figure 4.16, the majority of the patients, both survivors and non-survivors, had albumin values lower than the normal lower limit, which suggests the presence of albuminemia. This behavior confirmed that low albumin levels were presented in critically-ill patients [54].

Table 4.14 shows the best regression models for the albumin ratios and rates of change. Although the c-statistics for the ratios in T_1, T_2, and T_3 showed better results ($0.58 \leq c \leq 0.79$) than the statistics for the rates of change ($0.39 \leq c \leq 0.52$) in the same intervals, the sample sizes of the ratios for this parameter were smaller than the sample sizes for the same metric applied to other parameters, where at least 200 values for the ratios were used for analysis. In this case, the sample sizes for the ratios with albumin were, 18, 17, and 10 for r_1, r_2 and r_3, respectively.

Therefore, the results were not conclusive and more data will need to be available to make any statement regarding this parameter. .Is important to note that the measure of albumin is not common and that a similar situation was found with the VA dataset. In that case the sample size of albumin only allowed the calculation of 8 ratios, because only 15 patients had albumin values registered.

Table 4.14. Logistic regression models for albumin. Rc_i, rates of change; r_i, ratios

			Intercept	x	Odds ratio		c-statistic
					Point estimate	95%CI	
MIMIC II dataset	Rc_i	Rc_1	0.6124	4.9879	146.6	[<0.001, >999]	0.39
		Rc_2	0.5848	16.476	>999	[<0.001, >999]	0.52
		Rc_3	0.6188	9.658	>999	[<0.001, >999]	0.46
	r_i	r_1	-0.1843	0.8435	2.324	[0.030,181.582]	0.58
		r_2	8.8479	-8.3005	<0.001	[<0.001, >999]	0.63
		r_3	-8.6031	8.6340	>999	[0.055, >999]	0.79

Two sample t-tests between mean rates of change and mean ratios showed that none of them can differentiate survivors from non-survivors (0.09< p-values<0.71). This result may be due to the high variability presented in the albumin values and confirmed that the albumin levels in critically-ill patients did not show notorious differences between survivors and non-survivors, as was shown in Figure 4.16.

4.1.5.3 Total CO_2 Analysis – MIMIC II Dataset

A total of 1,685 patients from the MIMIC II dataset were analyzed, including 843 survivors and 842 non-survivors. Those patients had at least two measures registered during the period of analysis. This sample contained 1,697 admission cases and 16,120 measures. The mean TCO_2 value was 24.94 ± 4.27 mEq/L (95% CI = [24.84, 25.04]) and 24.42 ± 5.29 mEq/L (95% CI = [24.31, 24.53]) for survivors and non-survivors, respectively. Figure 4.17 shows the general behavior of the TCO_2 data over time for a sample of 30 admission cases.

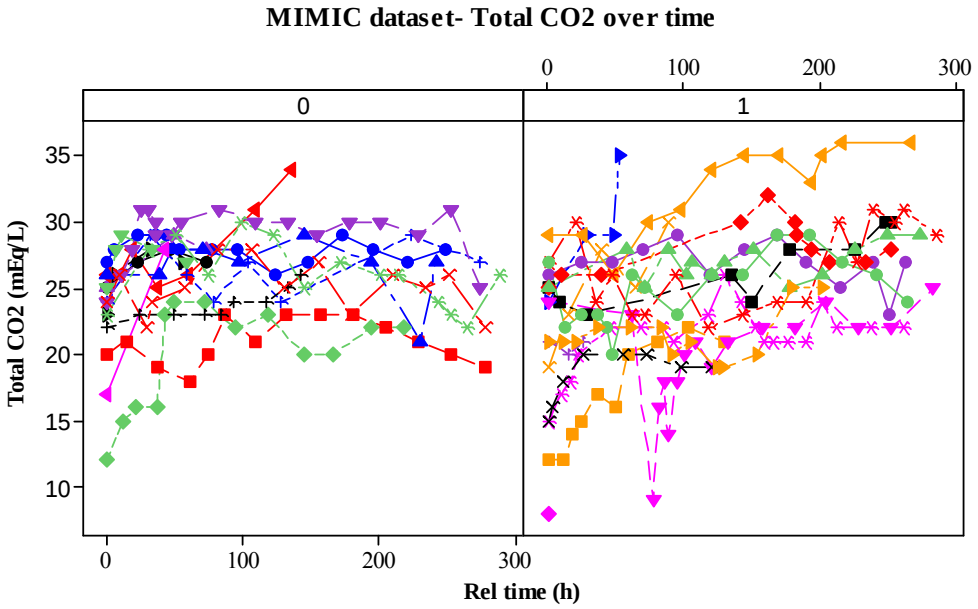


Figure 4.17. Total CO_2 data over time - MIMIC II dataset

In Figure 4.17 we cannot observe a clear difference between survivors and non-survivors. However, some of the non-survivors had TCO_2 values less than 23 mEq/L, the lower limit for the common "normal" range [44].

Table 4.15 shows the best regression models for the ratios and rates of change applied to total CO_2. It can be seen that the c-statistics for all models with total carbon dioxide were smaller than the statistics with calcium or platelet count applied to the same dataset.

Table 4.15. Logistic regression models for TCO_2. Rc_i, rates of change; r_i, ratios

			Intercept	x	Odds ratio		c-statistic
					Point estimate	95%CI	
MIMIC II dataset	Rc_i	Rc_1	0.0961	-0.0914	0.913	[0.383,2.177]	0.51
		Rc_2	0.0971	-0.7499	0.472	[0.099,2.255]	0.51
		Rc_3	0.0900	-0.9573	0.384	[0.069,2.133]	0.50
	r_i	r_1	0.5933	-0.3884	0.678	[0.260,1.770]	0.51
		r_2	0.7472	-0.4667	0.627	[0.220,1.784]	0.52
		r_3	0.8132	-0.4470	0.640	[0.240,1.706]	0.54

The best results shown in Table 4.15 were for ratios in T_2 and T_3, where c-statistics were 0.52 and 0.54, respectively. Two sample t-tests between mean rates of change and mean ratios showed that none of the metrics can differentiate survivors from non-survivors (0.27< p-values<0.83).

It is important to note that the measure of total carbon dioxide is usually accompanied with the computation of the anion gap, since together they provide physicians with more information to diagnose or treat any acid-base imbalance. The most common disorder is metabolic acidosis, which usually occurs if the body produces too much acid or loses too much bicarbonate. Acidosis is reflected in the low pH level of blood and tissues. In the next sub-section, the anion gap is analyzed to evaluate if this parameter can provide prognostic information. This and other implications derived from the analysis of anion gap levels and low total carbon dioxide is discussed in Section 4.2.

4.1.5.4 Anion Gap Analysis – MIMIC II Dataset

A total of 1,564 patients from the MIMIC II dataset were analyzed, including 789 survivors and 775 non-survivors. Those patients had at least two measures registered during the period of analysis. This sample contained 1,575 admission cases and 14,943 measures. The mean anion gap value was 13.6 ± 3.21 mEq/L (95% CI = [13.53, 13.68]) and 14.61 ± 4.01 mEq/L (95% CI = [14.52, 14.70]) for survivors and non-survivors, respectively. From the data, it can be seen that the means between survivors and non-survivors were different. Both confidence intervals for the means did not overlap. Therefore, it can be concluded that, on average, anion gap values for non-survivors were higher than the anion gap values for survivors. Figure 4.18 shows the general behavior of the anion gap data over time for 30 admission cases.

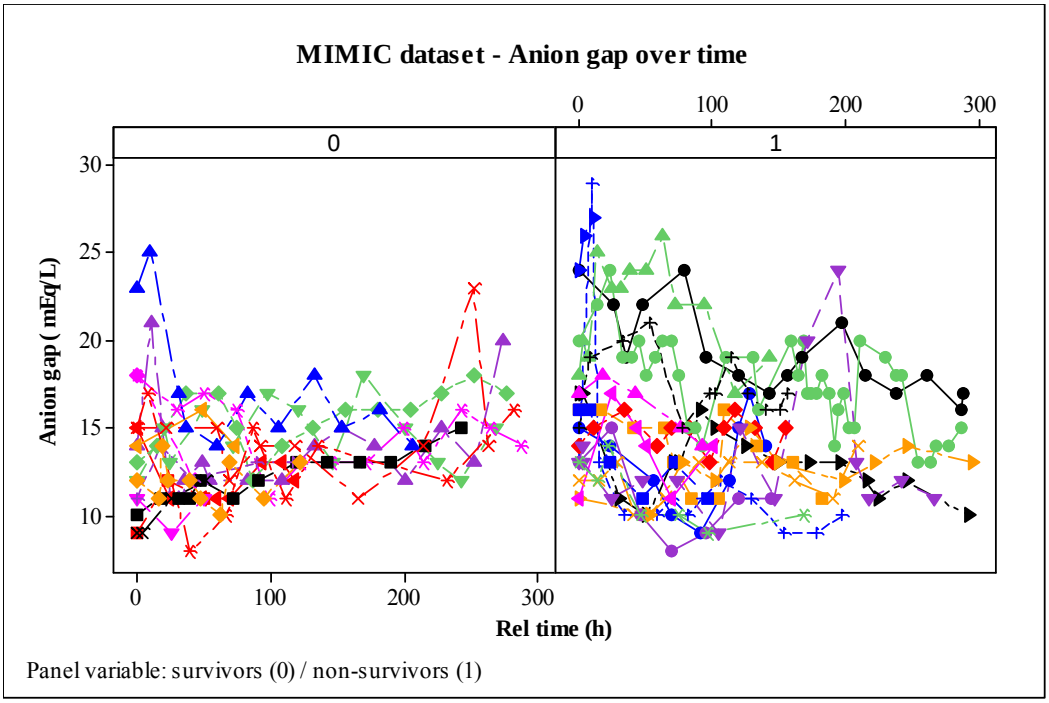


Figure 4.18. Anion gap data over time - MIMIC II dataset

The previous figure shows differences between survivors and non-survivors. First, non-survivors usually presented higher anion gap values than survivors. Second, the variability in non-survivors was higher than the variability presented in survivors.

In general, it also was seen that several patients had anion gap values greater than 16 (the upper limit for common "normal" ranges, estimated by colorimetric and flame photometry), an issue that suggests the presence of acidosis. Nevertheless, there were also patients that did not have "abnormal" anion gaps but did not survive. In the previous sub-section, total carbon dioxide was analyzed, and it was observed that most of the non-survivors showed low levels of carbon dioxide, whereas in Figure 4.18, it was observed that most of the non-survivors showed high anion gaps. This situation of having low levels of carbon dioxide (less than 23 mEq/L) and high levels of anion gap (more than 16 mEq/L) suggests the presence of a severe acidosis with increased anion gap, an illness that could be life-threatening.

Table 4.16 shows the results from the best regression models for the anion gap, where c-statistics were lower than the statistics with other parameters such as calcium and platelet count applied to the same dataset. However, the results in terms of c-statistic for the anion gap ratios and rates of change were very similar ($0.55 \leq c \leq 0.57$).

Table 4.16. Logistic regression models for anion gap. Rc_i, rates of change; r_i, ratios

			Intercept	x	Odds ratio		c-statistic
					Point estimate	95%CI	
MIMIC II dataset	Rc_i	Rc_1	0.0953	-1.533	0.216	[0.076,0.611]	0.56
		Rc_2	0.0793	-1.6601	0.190	[0.037,0.972]	0.55
		Rc_3	0.0767	-1.0403	0.352	[0.059,2.120]	0.56
	r_i	r_1	1.2424	-1.0318	0.356	[0.161,0.790]	0.57
		r_2	1.1648	-0.8835	0.413	[0.169,1.009]	0.55
		r_3	0.9750	-0.7040	0.495	[0.197,1.243]	0.56

Two sample t-tests between mean rates of change and mean ratios showed that ratios and rates of change for the intervals T_1 and T_2 can differentiate survivors from non-survivors, but the metrics in the interval T_3 could not, with p-value=0.134 for the ratio and p-value=0.243 for the rate of change. This result indicates that in intervals from 50 to 150 or 50 to 200 hours (between 4 and 6 days), the differences in anion gap between survivors and non-survivors were more notorious. It can also be seen that the odds ratio estimates in interval T_3 for both metrics, ratios and rates of change, were higher than the odds ratio estimates from the models developed for the same metrics in smaller intervals.

Appendix B provides the complete descriptive statistics and p-values for the differences in mean ratios and mean rates of change for all the parameters described in the current section. After reviewing the results for each parameter individually with the MIMIC II dataset, it can be seen that, although some of them show differences between survivors and non-survivors, the

results in terms of concordance measures was not as significant as the results obtained with the platelet count. In the following section, the impact of including simultaneously several parameters and their interactions in the results of the regression models are analyzed.

4.1.6 Multivariate Analysis – MIMIC II Dataset

From the previous sections, it was observed that none of the parameters performed as well as platelet count. However, the inclusion of some parameters simultaneously while analyzing the VA dataset showed that the predictive power of the models could be improved. Additionally, the results from the MIMIC II dataset suggested that ratios in T_2 and T_3 performed better than rates of change. The impact in using simultaneously different parameters were analyzed with ratios for T_2 and T_3. Table 4.17 shows the c-statistics and sample sizes for each regression model for ratios in T_2 and T_3 depending on the parameters included. From 26 possible models, considering the combination of 2, 3, 4 and 5 parameters, only 11 had sample sizes greater than 18; the other models had sample sizes lower than 6, which does not allow the development of a reliable model.

Table 4.17. C-statistics and sample sizes for models with ratios r_i

Parameters in the model	r_2		r_3	
	Sample size	**c-statistic**	**Sample size**	**c-statistic**
PLT, Ca	82	0.618	56	0.569
PLT, AG	127	0.633	87	0.614
PLT, TCO_2	42	0.642	92	0.590
TCO_2, AG	31	0.701	53	0.604
PLT, Ca, TCO_2	22	0.924	37	0.765
Ca, TCO_2, AG	18	0.854	25	0.715
PLT, Ca, AG, TCO_2	18	0.889	25	0.760
Ca, TCO_2	22	0.848	37	0.718
Ca, AG	51	0.671	38	0.623
PLT, Ca, AG	51	0.662	38	0.694
PLT, TCO_2, AG	31	0.707	53	0.636

The first seven models presented for ratios in T_2 were statistically valid and some of their parameters were significant; the analysis of maximum likelihood estimates showed significance for some of the parameters (p-value<0.06), and the global null hypothesis testing (Chi-square test) also showed significance (p-value<0.06). However, the last four models did not show significance nor did the models developed with ratios in T_3.

Throughout the previous results, it can be seen that the inclusion of some parameters in the model enhanced its performance in terms of the c-statistic—being the best model, which includes platelet count, calcium, and total carbon dioxide (c=0.92). Figure 4.19 presents the ROC curve for this model. It can be seen that the curve follows the left-hand border and then the top border, showing the accuracy of the classification model.

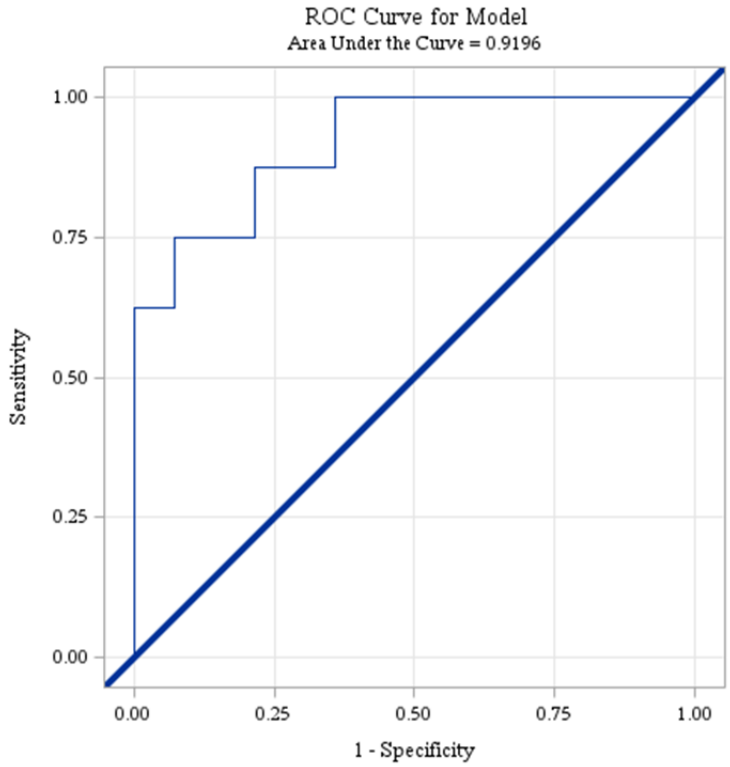


Figure 4.19. ROC curve for the model with Ca, PLT and TCO_2 - MIMIC II dataset

The maximum likelihood ratio for this model presented a p-value=0.002, whereas the different estimates vary, with calcium (p-value=0.02) the most significant. Carbon dioxide (p-value=0.07) and platelet count (p-value=0.07) may be not significant at 5%.

A similar situation was observed for the model that includes platelet count, calcium, anion gap, and total CO_2. The maximum likelihood ratio presented a p-value=0.02, and the most significant parameter was calcium (p-value=0.05), but the other parameters were not statistically significant ($0.1 \leq$ p-value ≤ 0.39). When analyzing the model with calcium, anion gap, and total carbon dioxide, then the maximum likelihood ratio showed a p-value of 0.06, but all the estimates were not significant ($0.1 \leq$ p-value ≤ 0.18). It can be concluded that although the c-statistic may be improved considering several parameters simultaneously in the model, the inclusion of those parameters in the model may not necessarily be significant. Appendix D provides the models developed, including the parameters estimates, point estimates, and 95% CI for the odds ratios.

In Section 4.1.4.3, modeling was discussed by analyzing various parameters simultaneously and as well as the impact of adding interaction terms into those models. It was concluded in the case of rates of change that the performance of the model was improved. Therefore, the best models were selected from Table 4.17 and the models interaction terms were developed.

First, the model that includes platelet count, calcium, and total carbon dioxide was selected, because it was the model that provided a better c-statistic. However, the maximum likelihood estimates could not be computed because the data points were separated. Second, the model that includes platelet, calcium, total carbon dioxide, and anion gap was selected, and the results were similar. No maximum likelihood estimates could be computed. Third, the model

with calcium, total carbon dioxide, and anion gap was reviewed. In this case, the c-statistic was improved from 0.85 to 0.86. However, the analysis of maximum likelihood showed that none of the interactions were significant (p-value $\geq$ 0.32). Finally, the model that includes calcium and total carbon dioxide was selected. In this case, the c-statistic improved from 0.84 to 0.85, but, again, the interaction term was not significant (p-value=0.33). It can be concluded that the interaction terms in the classification models do not add value to the result. Appendix C presents the complete regression models from these cases.

In the present analysis of various parameters, the sample sizes were too small to apply the bootstrapping methodology to evaluate the sensitivity of the estimates. In the following section, the results are discussed and compared with the results obtained by previous similar studies. The platelet count analysis is discussed first, comparing the results from both datasets. The addition of other parameters and the corresponding multivariate analysis with the VA dataset is then reviewed. Finally, other parameters from the MIMIC II dataset were also analyzed, individually and simultaneously. A discussion of these results and their impact in patient monitoring is presented.

4.2 Discussion

4.2.1 Platelet Count Analysis

The data mining approach conducted has shown the changes over time of the platelet count for two different cohorts: a homogeneous population from the VA dataset and a heterogeneous population composed of ICU patients from different hospitals, conditions, and diseases. Both datasets were selected, because the objective is to generalize the methodology to the broader and heterogeneous population. Both datasets were compared using two metrics: rate

of change as determined by multiple point regression and by the simpler fixed-time platelet value ratios at specific time intervals. Both datasets demonstrated that the metrics (rates of change and ratios) are comparable and can differentiate survivors from non-survivors, and, moreover, that the results are comparable. That means that a simple fraction between two specific measures can be used to estimate the probability of having an adverse event, providing a warning that could aid the physicians' decision making process.

The result in terms of concordance measures (c-statistic) for the homogeneous population was better than other results found in the literature using other similar metrics and even risk assessment scores that involved several other parameters, not only related to the circulatory system, but also to respiratory, nervous, and cardiovascular systems, among others. Most of those risk scores use at least 12 parameters [34, 57]. It is important to note that several studies suggest that thrombocytopenia in critically-ill patients is a marker of illness severity, and some risk assessment scores (e.g., SOFA or APACHE II) support this issue by reporting higher scores in these types of patients than in patients who were admitted with normal platelet values to the ICU [47]. The c-statistics from the models with the MIMIC II dataset were lower than the c-statistics from the VA dataset, as would be expected due to the heterogeneity and variability presented in the data.

The time intervals were chosen after observing that platelet counts fall promptly after an acute event and then variably return toward a normal level, allowing an important marker to be defined for this critical episode of the care cycle. The biphasic course observed in this study has been reported in previous studies that studied patients after surgery [55] and patients with acute myocardial infarction [56]. The upper limit of the intervals used for the analysis was 200 hours (approximately 8 days). Longer intervals were not used because they were not considered

prognostically useful for a timely intervention or decision early in a patient's care cycle. However, time in clinical decision-making for critically-ill patients is vital, and the use of a single metric as a ratio of values at two time points could be more beneficial in this setting. Thus, it has been demonstrated that the ratios using only 2 measures over a specific interval, such as 75 to 150 or 75 to 200 hours (~3 to 5 days), can provide prognostic information comparable to using the formal rate of change over the same interval.

After statistically comparing both datasets, it can be concluded that the models for the ratios in T_2 (50 to 150 hours) and T_3 (50 to 200 hours) show the best performance for the MIMIC II dataset and a very good performance for the VA dataset. Therefore, the ratios for T_2 and T_3 can be used to analyze changes over time in platelet count, providing a dynamic patient profile that may improve the management of these complex processes. It also has been demonstrated that ratios in T_5 (75 to 150 hours) and T_6 (75 to 200 hours) can discriminate outcomes as well as the rate of change in a homogeneous population (the VA dataset), both having a c-statistic of 0.78. This result is better than the result from APACHE II score (c=0.72), the rate of change per day (c=0.74) analyzed by Nijsten *et al.* [32], and the results from Strauss *et al.* [47], who used a drop in platelet count percentage as metric in a prospective study (c=0.75) and compared the results with APACHE II (c=0.73) and the Sequential Organ Failure Assessment score - SOFA (c=0.73) [56].

4.2.2 Multivariate Analysis – Platelet Count, Calcium and MPV- VA Dataset

First, mean platelet volume was analyzed independently and was found to have none of the metrics that could differentiate survivors from non-survivors. Also, the c-statistics from the prediction models were very low ($c \leq 0.53$). However, 95% CI for the mean values did not overlap, suggesting that there should be a difference between MPV values of survivors and non-

survivors. Additionally, calcium was analyzed independently and differences were seen between survivors and non-survivors. Although the mean values were similar, an increasing trend for survivors was seen, while almost a plateau was seen for non-survivors. After comparing the models developed for the metrics, the best results were for rates of change for T_2 (c=0.79) and T_3 (c=0.80), differentiating both survivors from non-survivors.

Using platelet count, calcium, and mean platelet volume, a first multivariate analysis was conducted with the ratio for T_2 (c=0.75). This result was similar to the result obtained for platelet count and better than the result obtained independently for calcium and mean platelet volume using the same ratio.

Mean platelet volume was combined with platelet count as platelet mass. As a result, the behavior of platelet mass between survivors and non-survivors showed more differences; 95% CI for the mean platelet mass was [1820.6,1865.1] $x10^{-6}$ and [1599.5,1696.8]$x10^{-6}$ for survivors and non-survivors, respectively. It can be concluded that the use of platelet mass highlights the differences between survivors and non-survivors and may be a good marker to consider if the measure of mean platelet volume is available.

The methodology was first applied for platelet mass independently, improving the results with respect to the results from the platelet count using the rates of change for T_2 (c=0.77) and T_3 (c=0.78). The multivariate analysis was conducted again using calcium and platelet mass. The results were improved for the rate of change in T_2 (c=0.83) and ratio in T_2 (c=0.75). From these results, it can be concluded that the combination of platelet count and mean platelet volume enhances the performance of the models and that the application of the same methodology with calcium and mean platelet mass may improve the predictive power of the models in a homogenous population as the VA dataset.

Finally, interaction terms were added into the classification models and, as a result, in both cases, rates of change and ratios, the c-statistic was improved. However, only in the case of the rate of change was the interaction term significant, and its inclusion as part of the classification model should be considered. In the following section, the results obtained with the MIMIC II dataset are discussed.

4.2.3 Analysis of other Parameters - MIMIC II Dataset

The methodology to analyze other parameters from the MIMIC II dataset was applied to calcium, albumin, anion gap and total CO_2. Those parameters have shown, through previous studies, that they could influence clinical outcomes in critically-ill patients. As reviewed in Chapter 2, several conditions, such as hypocalcemia, metabolic acidosis, or hypoalbuminemia, are present in ICU patients. In this study, each of those parameters was analyzed independently and then simultaneously. Predictive models with each parameter were constructed and assessed, and then models with more than one parameter were constructed and analyzed.

The behavior of the calcium values using the MIMIC II dataset was similar to the behavior seen with the homogeneous dataset from the VA. However, the differences between survivors and non-survivors were not as notable as for the VA population. In all cases, a drop was seen (calcium values less than 8.5 mg/dL), but the lowest calcium levels were seen for non-survivors. The recovery regarding calcium levels for survivors was quicker than the recovery for non-survivors. The result confirms the results obtained from previous studies that have used calcium as a marker for anticipating patient outcome. In this heterogeneous population, independent of the disease, the drops for non-survivors are lower than 8 mg/dL, which confirms the result from Zilvin *et al.* [40], who found that hypocalcemia (low levels of calcium) was present in around 88% of the patients included in his study. His sample was composed of 99

patients admitted to 7 different ICUs (medical, surgical, and burn, among others), but his study could not find a correlation between hypocalcemia and any specific illness. He only concluded that the hypocalcemia correlates with the severity of the illness.

Albumin was analyzed. The behavior of the albumin values did not show a notorious difference between survivors and non-survivors. However, mean values for non-survivors were lower than the mean values from survivors, indicating that the risk of complications is higher when albumin levels are low [36]. A similar situation was seen in a study conducted with elderly patients (more than 70 years of age) who were receiving mechanical ventilation, which reported lower albumin levels for non-survivors than survivors and concluded that low albumin level is an independent risk factor [54]. Finally, a meta-analysis that study hypoalbuminemia in acute illness concluded that this condition was a dose-dependent, "*an independent risk factor for poor outcome in the acutely ill*", including mortality and morbidity [58]. Of note is that albumin testing is usually performed for specific diseases such as renal disease, but it is not as common as calcium and platelet counts in routine blood tests. The albumin sample sizes in this study were smaller (between 10 and 18 units) than the sample sizes of the other parameters; the results suggest a correlation between low levels of albumin and mortality, but they are not conclusive and further studies will need to be conducted to analyze the influence of this parameter in clinical outcomes.

The results for total carbon dioxide were similar than the results for albumin; no notable difference could be seen between survivors and non-survivors. Nevertheless, lower values of carbon dioxide were seen for non-survivors, causing probably imbalances in the patient's electrolytes [44]. Total carbon dioxide is one of the parameters associated with acid-base imbalances, but to characterize these imbalances, usually other parameters are measured, such as

the anion gap or the pH, which measures the acidity or alkalinity in the blood. Low levels of total carbon dioxide result from either metabolic acidosis or as a compensation to respiratory alkalosis [59]. The ratios and the rates of change calculated with TCO_2 could not differentiate survivors from non-survivors, and the predictive power of the models constructed was poor ($c \leq 0.54$).

The last parameter from the MIMIC II dataset analyzed was the anion gap. The results showed differences in mean and variability between survivors and non-survivors. Higher anion gaps (more than 16 mEq/L) and higher drops in anion gap were presented in non-survivors, which may be a signal of metabolic acidosis [60, 61] or any malfunction of the kidney or lungs. The ratios and rates of change for T_1 and T_2 could differentiate survivors from non-survivors. However, as stated previously, anion gap is used with other parameters such as the total carbon dioxide, and the behaviors analyzed simultaneously have been shown to provide more information regarding acid-based disorders.

There are studies that use a delta gap, which is the ratio of the variation in anion gap over the variation in bicarbonate, measured through the total carbon dioxide [62]. Further studies analyzing both parameters may provide more information, allowing a better understanding of these conditions and their impact in patient outcome.

The performance of the models using each parameter independently was not better than the performance seen for platelet count, with the exception of albumin. In this case, the sample sizes were smaller (less than 18 values) than the sample sizes used for the other parameters. The best models were calcium ratios for T_2(c=0.56) and T_3(c=0.60), anion gap ratios for T_1(c=0.57) and T_3(c=0.56), TCO_2 ratios for T_2(c=0.52) and T_3(c=0.55), and albumin ratios for T_2(c=0.64) and T_3(c=0.79).

A multivariate analysis with different combinations of all parameters with ratios in T_2 and T_3 was conducted to evaluate if the results could be improved. Effectively, the addition of some parameters in the models improved the results in terms of concordance measures; however, the sample sizes were reduced in comparison to the sample sizes of individual parameters. When analyzing maximum likelihood estimates, some parameters are not significant in the models.

The best model developed was the model that includes calcium, platelet count, and total carbon dioxide ratios for the intervals T_2(c=0.92) and T_3(c=0.76). It was observed that the combination of calcium, platelet count, and TCO_2 improved the predictive power of the model. The sample sizes were reduced to 22 and 37 cases for r_2 and r_3, respectively; however, the model parameters were statistically significant, with p-value=0.0021 for the likelihood ratio test. Therefore, the ratios for T_2 may be used to simultaneously analyze changes over time in calcium, platelet count, and TCO_2 and may be used as input for a predictive model, which could provide useful and prognostic information for care providers.

Finally, interaction terms were added into the best models for ratios in the intervals T_2 and T_3; as a result, none of the interaction terms were significant, although in most of the cases the c-statistics were improved. All these results of applying models with several parameters suggest that the dynamism of the physiologic parameters studied could be captured through the metrics developed. However, further prospective studies should be conducted with bigger sample sizes to be conclusive and validate those models. The following chapter presents the conclusions derived from the previous discussion and the impact of the results in the patient monitoring process.

CHAPTER 5: CONCLUSIONS, LIMITATIONS AND FUTURE WORK

The data mining approach has shown that the changes over time of specific physiologic parameters in critically-ill patients provide prognostic information and could aid physicians in their decision-making processes. Specific parameters such as platelet count, calcium, and anion gap have different behaviors or patterns in survivors and non-survivors. A methodology was developed to simultaneously analyze important physiologic parameters in specific time intervals as short as four to six days after the second day of being admitted to an ICU. This method allows the stratification of retrospective patient care data under uncertain conditions of the specific diagnosis and the onset of the acute event, allowing predictive modeling with satisfactory accuracy to assist physicians in anticipating changes in recovery trajectories, allowing alterations in the patient management.

Two methods of establishing rate of change (discrete point and regression on continuous data) were compared. Both metrics were comparable, differentiated survivors from non-survivors, and, in homogeneous populations, were more predictive than more complex metrics and risk assessment scores with greater dimensionality. It also was demonstrated that the methodology could be applied to a heterogeneous population using changes over time in platelet count with satisfactory results, comparable to the results from the homogeneous dataset.

Platelet count and calcium may provide prognostic information during the first 250 hours after ICU admission. Platelet count dropped below $150x10^9$/L (common normal range) for the majority of the patients and then normalized or rose above this value during the first 200 hours.

A similar behavior was seen for calcium, but in this case the calcium for survivors stabilized during the first 150 hours, whereas non-survivors did not show a specific pattern.

The use of calcium rates of change for a homogeneous population allowed the improvement of the predictive power of the regression models in T_2 (c=0.79) and T_3 (c=0.80). These results confirmed that calcium in blood (plasma calcium) is an important physiological marker to anticipate adverse events in critically-ill patients and should be included in any predictive model used for patient monitoring. Furthermore, combining mean platelet volume and platelet count as platelet mass, the results of the models using rates of change for T_2 (c=0.77) and T_3 (c=0.78) were improved. However, mean platelet volume is not always included as part of a complete blood count test, and its use as a potential marker combined with platelet count should be analyzed considering other factors such as availability and cost. It was demonstrated that the use of platelet mass and calcium rates of change for T_2, improves the performance of the predictive model (c=0.83).

In a heterogeneous population, the rate of change determined by simpler fixed-time parameter value ratios applied to platelet count, calcium, albumin, anion gap, and total carbon dioxide was demonstrated to have better predictive power than the rate of change determined by multiple point regression. This situation should be due to the high variability of the data and heterogeneity of the population of the MIMIC II dataset. It was observed that platelet count in the heterogeneous population was the best predictor of adverse outcomes among all the parameters evaluated. This result suggests that this parameter should be considered in critically-ill patient monitoring processes during recovery trajectories.

The independent behavior of total carbon dioxide and albumin did not show notable differences between survivors and non-survivors. However, the anion gap showed differences between survivors and non-survivors in short time intervals (50 and 100 hours) after the first 50 hours of ICU admission. The anion gap presented more variability for non-survivors and also greater values than the anion gap values for survivors. Therefore, in those models developed specifically for each parameter, the statistics associated with concordance measures were not sufficiently predictive. Nevertheless, the simultaneous analysis of two or more parameters improved the predictive power of those models, but reduced the sample sizes.

The models developed for the heterogeneous population, including calcium, total carbon dioxide, and platelet count ratios for T_2 and T_3, were more predictive (c=0.92) than models using complex metrics such as SOFA or APACHE II. Nevertheless, the results are based on sample sizes that are smaller ($18 \leq N \leq 82$) than the sample sizes used for each parameter individually ($192 \leq N \leq 533$), with the exception of the albumin test ($10 \leq N \leq 18$), which is not conducted as frequently as the other tests. The previous results suggest that the simultaneous use of simple ratios between two point values of the previous parameters in a short interval of four days may provide prognostic information.

It was also observed that the inclusion of interaction terms in the classification models did not add any value to the results. Although in some cases, the c-statistics for the models were improved, the interactions between parameters were not significant in those models and, in other cases, no maximum likelihood estimates could be calculated due to the small sample size and because the data points were completely separated. This is evidence of the high variability presented in these complex physiologic parameters.

Being a retrospective study, the fact that interventions could not be implemented and assessed was an unavoidable limitation. Other limitations, specifically to the MIMIC II dataset, were the heterogeneity of the population, the differing stages of disease, and the variability regarding the recorded data, as it contains platelet measures registered before or after ICU admission and around 15% of the population had unknown ICU admission time and dates. In this case, the synchronization of the patient care cycle was not as simple as for the VA dataset, where the reference event for all patients was the date and time of surgery. For the MIMIC II data, it was assumed that the first platelet value and the minimum platelet value of the ICU patients were realistic surrogates for the time of the reference event or acute event, which may not be an accurate assumption in some cases. This critical assumption was substantiated by the results, which are comparable with the results from the homogeneous VA dataset. This assumption was extended to other parameters: calcium, albumin, anion gap, and total CO_2 and demonstrated that multivariate analysis, which includes hidden interactions between the parameters, improves the results considerably in terms of concordance measures ($0.62 \leq c \leq 0.92$). Finally, considering the limitations associated with a retrospective study, a further prospective study is needed to validate the results to be applicable for new ICU patients.

To summarize, the most relevant findings of this research are the following:

- Changes over time of platelet count, calcium, anion gap, albumin, and total carbon dioxide in critically-ill patients may provide prognostic information.
- Platelet count, calcium, and anion gap show different behaviors or patterns in survivors and non-survivors.
- Rates of change in calcium in a homogeneous population provide a better classification model with more predictive power than platelet count.

- In a heterogeneous population, platelet count performed better as predictor of patient outcome than calcium, anion gap, albumin, and total carbon dioxide independently.
- The combination of mean platelet volume with platelet count as platelet mass enhances the predictive power of the classification model.

In conclusion, the most relevant contributions and impact of this research are the following:

- The presented methodology could be generally applicable to ICUs and critically-ill patients, if at least two measures (ratio) or a small set of them (rate of change) of specific parameters in a short time frame (four to six days after two days of ICU admission or acute event) are available.
- The metrics developed (ratios and rates of change) are comparable and they differentiate survivors from non-survivors and are more effective than complex metrics and risk assessment scores with greater dimensionality such as APACHE II and SOFA applied to a homogeneous population.
- A new method of synchronization or alignment of the patient care cycle was provided.
- The methodology is potentially extensible to other parameters with high levels of variation in short periods of time, providing an advantage over the classical use of times series when dealing with small sample sizes per patient.
- This method allows the stratification of retrospective patient care data under uncertain conditions of the specific diagnosis and at the onset of an acute event, allowing predictive modeling with satisfactory accuracy to assist physicians in anticipating

changes in recovery trajectories, allowing alterations in patient management, and leading to more personalized patient care and reduced mortality rates.

This research has contributed to the analysis of important and complex physiologic parameters, providing a methodology to analyze them and capture their dynamism through simple and proven metrics. However, there are still several unknown relationships among those physiologic parameters that need to be investigated. It also has been demonstrated that the changes over time of those parameters may provide prognostic information to care providers. Considering the high levels of mortality due to critical illnesses, it is important to continue working on a better understanding the behavior of those parameters to improve patient care.

Future work research efforts should be focused on:

- Combining parameters into a single metric. This may provide enhanced support to physicians with a simplified metric in anticipating potential adverse outcomes during the patient recovery process.
- Stratifying patients by disease or by specific conditions to homogenize the population and improve the performance of the models, as was demonstrated by using the VA dataset.
- Investigating the behavior of anion gap and its relationship with total carbon dioxide, perhaps considering that the presence of fluid imbalances is a common disorder among ICU and critically-ill patients. Metabolic acidosis could be life-threatening, and this research and other studies suggest that both physiologic signals are correlated with increased mortality.

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APPENDICES

Appendix A Sensitivity Analysis with Bootstrapping - 100 Replicates

Table A.1. Parameter estimates - PLT count in $T_{2,}, T_3, T_5$ and T_6. Ratios r_i, rates of change Rc_i

Dataset	Metric	Sample size	Parameter	Estimate (regression model)	Estimate (Bootstrapping)	SD (Bootstrapping)	95%CI
VA	r_2	180	Intercept	1.33	1.27	1.01	[-0.35,3.90]
			PLT	-2.21	-2.23	0.78	[-4.07,-1.07]
	r_3	120	Intercept	1.32	1.34	0.97	[-0.61,3.56]
			PLT	-1.62	-1.65	0.57	[-2.94,-0.64]
	r_5	180	Intercept	2.12	2.14	1.15	[0.22,4.28]
			PLT	-2.77	-2.79	0.83	[-4.68,-1.52]
	r_6	180	Intercept	1.19	1.22	1.09	[-0.94,3.59]
			PLT	-1.59	-1.66	0.65	[-2.94,-0.51]
	Rc_2	280	Intercept	-1.19	-1.20	0.32	[-1.81,-0.57]
			PLT	-1.53	-1.53	0.43	[-2.34,-0.77]
	Rc_3	340	Intercept	-0.88	-0.86	0.29	[-1.41,-0.30]
			PLT	-1.63	-1.67	0.34	[-2.30,-1.18]
	Rc_5	250	Intercept	-1.02	-1.00	0.33	[-1.67, -0.36]
			PLT	-1.41	-1.43	0.36	[-2.37,-0.87]
	Rc_6	250	Intercept	-0.70	-0.68	0.42	[-1.61,0.18]
			PLT	-1.56	-1.59	0.42	[-2.43,-0.92]
MIMIC II	r_2	350	Intercept	-0.03	0.00	0.39	[-0.67,0.87]
			PLT	-1.12	-1.14	0.34	[-1.85,-0.54]
	r_3	250	Intercept	-0.40	-0.38	0.36	[-1.04,0.49]
			PLT	-0.64	-0.66	0.27	[-1.29,-0.21]

Appendix B Descriptive Statistics and p-values for the Differences in Mean

Table B.1. MPV r_i and Rc_i - VA dataset - Descriptive statistics. S, survivors; NS, non-survivors

r_i	r_1		r_2		r_3	
	S	NS	S	NS	S	NS
Sample size	181	10	136	9	92	6
Mean	0.9984	1.0110	0.9742	0.9755	0.9660	0.9633
Standard Deviation	0.0662	0.0647	0.0812	0.0710	0.0920	0.1030
p-value		0.571		0.959		0.953
Rc_i	Rc_1		Rc_2		Rc_3	
	S	NS	S	NS	S	NS
Sample size	239	14	244	14	247	14
Mean	0.0007	-0.0082	-0.0034	-0.0044	-0.0037	-0.0028
Standard Deviation	0.0162	0.0350	0.0099	0.0104	0.0088	0.0078
p-value		0.361		0.731		0.638

Table B.2. Ca r_i and Rc_i - VA dataset - Descriptive statistics. S, survivors; NS, non-survivors

r_i	r_1		r_2		r_3	
	S	NS	S	NS	S	NS
Sample size	184	10	136	10	86	7
Mean	1.0346	1.0289	1.0625	1.0115	1.0552	0.9888
Standard Deviation	0.0753	0.0660	0.0867	0.0978	0.0845	0.1023
p-value		0.797		0.140		0.142
Rc_i	Rc_1		Rc_2		Rc_3	
	S	NS	S	NS	S	NS
Sample size	253	15	246	15	250	15
Mean	0.0125	0.0058	0.0058	-0.0024	0.0054	-0.0016
Standard Deviation	0.0353	0.0339	0.0081	0.0080	0.0071	0.0072
p-value		0.451		0.002		0.002

Table B.3. PLT mass r_i and Rc_i - VA dataset - Descriptive statistics. S, survivors; NS, non-survivors

r_i	r_1		r_2		r_3	
	S	NS	S	NS	S	NS
Sample size	181	11	136	10	92	7
Mean	1.2435	1.1225	1.649	1.2776	2.0035	1.3967
Standard Deviation	0.3326	0.2857	0.5833	0.4720	0.9879	0.9300
p-value		0.2008		0.038		0.142
Rc_i	Rc_1		Rc_2		Rc_3	
	S	NS	S	NS	S	NS
Sample size	241	15	245	15	249	15
Mean	4.6521	-0.4699	6.9024	1.7796	7.8232	2.7541
Standard Deviation	8.4409	10.8100	6.8900	4.1520	6.1226	3.7000
p-value		0.092		0.000		0.000001

Table B.4. Ca r_i and Rc_i - MIMIC II dataset - Descriptive statistics. S, survivors; NS, non-survivors

r_i	r_1		r_2		r_3	
	S	NS	S	NS	S	NS
Sample size	160	191	110	141	84	108
Mean	1.0224	1.0189	1.027	1.0167	1.0432	1.022
Standard Deviation	0.0679	0.0939	0.0865	0.114	0.0878	0.1124
p-value		0.685		0.417		0.148
Rc_i	Rc_1		Rc_2		Rc_3	
	S	NS	S	NS	S	NS
Sample size	335	453	448	557	491	589
Mean	0.0019	0.0023	0.0018	0.0039	0.0019	0.0037
Standard Deviation	0.0280	0.0223	0.0119	0.0639	0.0097	0.0604
p-value		0.851		0.480		0.489

Table B.5. Albumin r_i and Rc_i - MIMIC II dataset - Descriptive statistics. S, survivors; NS, non-survivors

r_i	r_1		r_2		r_3	
	S	NS	S	NS	S	NS
Sample size	6	12	3	11	6	4
Mean	1.0178	1.0667	0.9376	0.8815	0.8635	1.0262
Standard Deviation	0.2145	0.2893	0.1259	0.0787	0.1689	0.0974
p-value		0.693		0.539		0.095
Rc_i	Rc_1		Rc_2		Rc_3	
	S	NS	S	NS	S	NS
Sample size	27	49	56	96	73	133
Mean	-0.0046	-0.0021	-0.0047	-0.0015	-0.0029	-0.0012
Standard Deviation	0.0337	0.0104	0.0213	0.0092	0.0191	0.0081
p-value		0.71		0.275		0.47

Table B.6. TCO_2 r_i and Rc_i - MIMIC II dataset - Descriptive statistics. S, survivors; NS, non-survivors

r_i	r_1		r_2		r_3	
	S	NS	S	NS	S	NS
Sample size	242	291	165	209	116	158
Mean	1.0592	1.0468	1.1034	1.0856	1.1417	1.115
Standard Deviation	0.1799	0.1769	0.19	0.1997	0.2472	0.2428
p-value		0.425		0.38		0.374
Rc_i	Rc_1		Rc_2		Rc_3	
	S	NS	S	NS	S	NS
Sample size	596	655	634	691	641	693
Mean	0.0198	0.0183	0.0165	0.0129	0.0144	0.0106
Standard Deviation	0.1161	0.1375	0.0633	0.0742	0.0575	0.0678
p-value		0.838		0.336		0.269

Table B.7. AG r_i and Rc_i - MIMIC II dataset - Descriptive statistics. S, survivors; NS, non-survivors

r_i	r_1		r_2		r_3	
	S	NS	S	NS	S	NS
Sample size	213	257	145	195	104	136
Mean	1.0504	0.9551	1.0096	0.9574	1.0322	0.9772
Standard Deviation	0.2335	0.2303	0.2567	0.2326	0.2838	0.2759
p-value		0		0.043		0.134
Rc_i	Rc_1		Rc_2		Rc_3	
	S	NS	S	NS	S	NS
Sample size	534	589	584	634	592	638
Mean	0.0105	-0.0123	0.0027	-0.0061	0.003938	-0.0003
Standard Deviation	0.1335	0.1228	0.0601	0.0870	0.05429	0.0723
p-value		0.003		0.039		0.243

Appendix C Regression Models with Interaction Terms

Table C.1. PLT mass and Ca r_2 - Regression model with interactions - VA dataset

	Estimates	Standard error	Wald Chi-square	Pr>Chi-square
Intercept	-11.555	11.9707	0.9317	0.3344
PLTmass r_2	13.063	12.1926	0.7601	0.3833
Ca r_2	10.629	9.1305	2.0460	0.1526
PLTmass r_2 * Ca r_2	-13.880	9.2168	2.2680	0.1321
c-statistic	**0.773**			

Table C.2. PLT mass and Ca Rc_2 - Regression model with interactions - VA dataset

	Estimates	Standard error	Wald Chi-square	Pr>Chi-square
Intercept	-2.044	0.3097	43.574	<.0001
PLTmass Rc_2	-0.081	35.624	2.178	0.1399
Ca Rc_2	-52.585	0.0428	3.621	0.0571
PLTmass Rc_2 * Ca Rc_2	-13.72	5.0494	7.389	0.0066
c-statistic	**0.867**			

Table C.3. AG, Ca and TCO_2 r_2 - Regression model with interactions - MIMIC II dataset

	Estimates	Standard error	Wald Chi-square	Pr>Chi-square
Intercept	65.996	123.0	0.288	0.5915
AG r_2	-166.00	159.8	1.078	0.2991
Ca r_2	-49.035	127.1	0.149	0.6997
TCO_2 r_2	42.019	42.086	0.997	0.3181
AG r_2 * Ca r_2	152.4	155.0	0.966	0.3256
AG r_2 * TCO_2 r_2	-3.749	31.986	0.013	0.9067
TCO_2 r_2 * Ca r_2	-46.347	51.718	0.803	0.3702
c-statistic	**0.861**			

Table C.4. Ca and TCO_2 r_2 - Regression model with interactions - MIMIC II dataset

	Estimates	Standard error	Wald Chi-square	Pr>Chi-square
Intercept	-58.722	45.615	1.657	0.1980
Ca r_2	59.941	43.187	1.926	0.1652
TCO_2 r_2	30.028	36.478	0.677	0.4104
TCO_2 r_2 * Ca r_2	-32.903	33.911	0.941	0.3319
c-statistic	**0.857**			

Appendix D Regression Models -Different Parameters - MIMIC II Dataset

Table D.1. PLT and Ca ratios in T_2 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-5.902	-	
PLT r_2	-0.351	0.704	[0.230, 2.151]
Ca r_2	5.048	155.74	[0.466, >999.9]
c-statistic	**0.618**		

Table D.2. PLT count and Ca ratios in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-3.023	-	
PLT r_3	-0.287	0.751	[0.313, 1.795]
Ca r_3	2.255	9.536	[0.014, >999.9]
c-statistic	**0.569**		

Table D.3. PLT count and TCO_2 ratios in T_2 - Regression model

		Odds ratio	
	Estimates	Point estimate	95%CI
Intercept	2.012	-	
PLT r_2	-1.034	0.356	[0.015,8.403]
TCO_2 r_2	-2.186	0.112	[0.008,1.600]
c-statistic	0.642		

Table D.4. PLT count and TCO_2 ratios in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-0.238	-	
PLT r_3	-0.232	0.793	[0.102, 6.158]
TCO_2 r_3	-0.473	0.623	[0.316, 1.228]
c-statistic	**0.590**		

Table D.5. AG and PLT count ratios in T_2 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	1.015	-	
PLT r_2	-2.077	0.125	[0.016, 0.990]
AG r_2	-0.323	0.724	[0.306, 1.711]
c-statistic	**0.633**		

Table D.6. AG and PLT count ratios in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-0.056	-	
PLT r_3	-0.505	0.604	[0.080, 4.552]
AG r_3	-0.505	0.603	[0.291,1.252]
c-statistic	**0.614**		

Table D.7. Ca and TCO_2 ratios in T_2 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-16.483	-	
Ca r_2	20.381	>999.999	[1.158,>999.9]
TCO_2 r_2	-5.363	0.005	[<0.001,3.505]
c-statistic	**0.848**		

Table D.8. Ca and TCO_2 ratios in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-1.087	-	
Ca r_3	3.209	24.77	[<0.001, >999.9]
TCO_2 r_3	-3.172	0.042	[<0.001,2.451]
c-statistic	**0.718**		

Table D.9. AG and Ca ratios in T_2 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-3.699	-	
Ca r_2	4.715	111.67	[0.100, >999.9]
AG r_2	-2.385	0.092	[0.004, 2.309]
c-statistic	**0.671**		

Table D.10. AG and Ca ratios in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	1.988	-	
Ca r_3	-1.777	0.169	[<0.001, >999.9]
AG r_3	-1.623	0.197	[0.004, 10.29]
c-statistic	**0.623**		

Table D.11. TCO_2 and AG ratios in T_2 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	2.077	-	
TCO_2 r_2	-0.115	0.891	[0.022, 36.82]
AG r_2	-3.234	0.039	[<0.001,4.000]
c-statistic	**0.701**		

Table D.12. TCO_2 and AG ratios in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	0.9887	-	
TCO_2 r_3	-0.436	0.646	[0.033, 12.575]
AG r_3	-1.777	0.169	[0.008, 3.661]
c-statistic	**0.604**		

Table D.13. PLT count, Ca and AG ratios in T_2 - Regression model

			Odds ratio
	Estimates	**Point estimate**	**95%CI**
Intercept	-4.338	-	
PLT r_2	0.594	1.813	[0.338, 9.730]
Ca r_2	5.15	172.7	[0.139, >999.9]
AG r_2	-2.93	0.053	[0.001, 1.976]
c-statistic	**0.662**		

Table D.14. PLT count, Ca and AG ratios in in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	2.727	-	
PLT r_3	-1.808	0.164	[0.013, 2.068]
Ca r_3	-1.433	0.238	[<0.001, >999.9]
AG r_3	-0.770	0.463	[0.007, 31.593]
c-statistic	**0.694**		

Table D.15. PLT count, Ca and TCO_2 ratios in T_2 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-20.18	-	
PLT r_2	-6.228	0.002	[0.002,<0.001]
Ca r_2	-30.936	>999.99	[46.774,>999.9]
TCO_2 r_2	-7.313	<0.001	[<0.001,<0.001]
c-statistic	**0.924**		

Table D.16. PLT count, Ca and TCO_2 ratios in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-2.907	-	
PLT r_3	-1.707	0.181	[0.018, 1.877]
Ca r_3	6.280	533.96	[0.005, >999.9]
TCO_2 r_3	-2.596	0.075	[0.002, 3.632]
c-statistic	**0.765**		

Table D.17. TCO_2, Ca and AG ratios in T_2 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-16.355	-	
Ca r_2	26.444	>999.9	[0.004,>999.9]
TCO_2 r_2	-6.749	0.001	[<0.001,6.271]
AG r_2	-5.618	0.004	[<0.001, 13.446]
c-statistic	**0.854**		

Table D.18. TCO_2, Ca and AG ratios in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	5.493	-	
Ca r_3	-0.313	0.731	[<0.001, >999.9]
TCO_2 r_3	-3.395	0.034	[<0.001, 24.69]
AG r_3	-3.113	0.044	[<0.001, 12.298]
c-statistic	**0.715**		

Table D.19. TCO_2, AG and PLT count ratios in T_2 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	3.460	-	
PLT r_2	-1.607	0.200	[0.008, 5.075]
TCO_2 r_2	-0.269	0.764	[0.018,33.298]
AG r_2	-3.111	0.045	[<0.001,5.535]
c-statistic	**0.707**		

Table D.20. TCO_2, AG and PLT count ratios in T_3- Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	1.4186	-	
PLT r_3	-0.4397	0.644	[0.282,1.464]
TCO_2 r_3	-0.1834	0.832	[0.039, 17.808]
AG r_3	-1.845	0.158	[0.007, 3.830]
c-statistic	**0.636**		

Table D.21. PLT count, Ca, AG and TCO_2 ratios in T_2 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	-17.54	-	
PLT r_2	-5.597	0.004	[<0.001, 14.99]
Ca r_2	31.360	>999.9	[0.755,>999.9]
AG r_2	-3.856	0.021	[<0.001,140.75]
TCO_2 r_2	-7.332	<0.001	[<0.001, 4.073]
c-statistic	**0.889**		

Table D.22. PLT count, Ca, AG and TCO_2 ratios in T_3 - Regression model

		Odds ratio	
	Estimates	**Point estimate**	**95%CI**
Intercept	6.256	-	
PLT r_3	-2.351	0.095	[0.002, 5.288]
Ca r_3	-1.726	0.178	[<0.001, >999.9]
AG r_3	-2.039	0.130	[<0.001, 138.51]
TCO_2 r_3	-1.518	0.219	[<0.001, 143.09]
c-statistic	**0.765**		

ABOUT THE AUTHOR

Monica Puertas earned her BS in Industrial Engineering in 1995 from the Pontificia Universidad Catolica del Peru (PUCP), pursued graduate studies in Quality and Environmental Management at the University of Reulingen–Germany (2001), and earned her MS in Industrial Engineering in 2002 from the University of Puerto Rico. She has more than 11 years of teaching, auditing, and consulting experience in quality and environmental management systems, including IS0 9001, ISO 14001, ISO 15189, ISO 17020, ISO/IEC 65, and ISO/IEC 17025. She has been an instructor, researcher, and teaching assistant in the Department of Industrial & Management Systems Engineering (IMSE) at the University of South Florida (USF) and the University of Puerto Rico-Mayagüez (UPRM) and a professor at the Pontificia Universida Catolica del Peru (PUCP). She has been lead auditor ISO 9000 (IRCA), internal auditor, and quality manager (Deutsche Gesellschaft für Qualität, Germany) and has been an examiner for the Peruvian National Quality Award (based on the Malcolm Baldrige National Quality Award). She worked for the Institute for Quality (PUCP) from 1995 until 2009, serving as Deputy Director during her last two years. Her research interests are related to systems modeling and optimization, data analysis in clinical settings, optimization of processes, and resource management in healthcare environments.