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Identification of Patient Recovery Patterns after Cardiovascular Surgery Based on Laboratory Tests Results

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Identification of Patient Recovery Patterns after Cardiovascular Surgery

Based on Laboratory Tests Results

by

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To my family and all my past, current and future students

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Abstract

In this dissertation is proposed a methodology to identify patient's recovery patterns after cardiovascular surgery based on laboratory tests results. The main purpose is to enhance the understanding of the manifestations of postsurgical complications in patients who underwent cardiovascular surgery. The analysis of patients' recovery process is based on the relationship between plasma calcium, ionized calcium and platelet count over time.

Laboratory results from the James A. Haley Veterans' Hospital databases, related to patients admitted to the Surgical Intensive Care Unit (SICU) after cardiac surgery (coronary artery bypass, aortic value replacement and mitral valve replacement), are used. These databases contain information regarding commonly ordered tests such as Complete Blood Count tests (CBC) and Basic Metabolic Panel (BMP) for a large group of patients over time. Physicians usually order these tests as a component of screening, routine evaluation, or serial assessment. These test results, contain a large amount of information used by most physicians during the diagnosis process and patient monitoring.

This study creates time series of some components of the aforementioned tests to analyze their behavior during the perioperative and postoperative period. Time series based clusters are developed to determine the similarities among tests results from four different types of patients: patients who had a satisfactory recovery process without any manifestation of complications, patients who experienced complications but survived,

patients who experienced complications and then died during their recovery and patients who died during the perioperative period. As a conclusion, the time series based clustering techniques were able to identify whether a patient is likely to fully recover from the surgery, but it does not have the power to detect effectively results corresponding to a patient experiencing complications.

The development of this methodology provides statistical evidence of the differences among different patterns on patient recovery. It is clear that patients experiencing complications have a steeper drop of test results after surgery, and also a non-stable trend towards normal levels. The appropriate use of the proposed methodology could help to timely anticipate complications in patient condition, improve the comprehensiveness of the assessment of patient condition based on laboratory test results and enhance the utilization of laboratory results databases.

Chapter 1: Introduction

One of the challenges faced by healthcare providers is to develop methodologies to effectively monitor patient condition during the cycle of care. The development of these methodologies is important, since their implementation could reduce patient mortality or improve their quality of life. This dissertation addresses the development of a methodology to effectively identify common patterns observed in laboratory test results over time of patients who underwent cardiovascular surgery. The focus of this study is the analysis of laboratory test results during the post-surgical period.

1.1 Background

It is estimated that diagnostic laboratory and imaging procedures represent the majority of healthcare costs in the U.S. The expenditures on imaging procedures doubled from $6.4 billion to $12.0 billion from 2000 to 2005 for just for Medicare's users [1]. Nevertheless, the amount of information that is currently extracted from laboratory test results is limited, due to the complexity of the interactions among them and the lack of effective methods to assist physicians interpreting them.

Still, laboratory tests are one of the primary sources of information to diagnose and monitor the patient's condition. Commonly physicians make inferences about patient condition based on the most recent test result, ignoring important factors such as the patient's tests history, relationships among different test results and their rate of change. Overall, physicians are not trained to perform diagnostics considering sets of multiple

attributes that describe a patient's condition. Yet, in many cases patients present complex health scenarios. In the general practice of medicine physicians lack techniques and tools that will help them detect temporal changes and hidden interactions among tests results. For the most part, physicians depend on their experience and their ability to interpret a set of laboratory results to best assess the patient's current condition, and its possible future state.

It is challenge for healthcare providers to improve the current utilization of tests results and imaging procedures to timely identify possible complications in a patient's condition. This is even more relevant for patients suffering from chronic diseases (i.e. heart disease) or patients with a compromised health condition such as those in intensive care units (ICUs).

It is estimated, just in the US, that more than five million patients are admitted to intensive care units yearly [2,3], being cardiovascular diseases and post-operatory management two of the primary causes. These two patient populations represent a large proportion of the deaths in the U.S.: 10% to 20% of the patients admitted in ICUs died in hospitals across the US [2, 3] and 34.3% of the total deaths in the US are caused by cardiovascular diseases [4].

1.1.1 Challenges in Interpreting Laboratory Test Results

There is a clear need to update current medical practices of monitoring patients to improve outcomes. Identification of postsurgical complications will help physicians to assess the likelihood of adverse outcomes, and then decide what interventions could improve the condition of the patient.

Unfortunately, physicians do not have means that allow them to do prospective assessment of the evolution of the patient. Based on their experience and results from different tests, physicians try to assess possible future events that could happen if no-interventions are done. Also, physicians are given a large set of indicators of patient condition (i.e. imaging results, laboratory work, clinical history, etc.) and it is difficult to fully extract all the information that is embedded to perform a comprehensive assessment of patient condition. There are several tests and the hidden relations among them are not easily recognized by the naked eye. It is necessary to develop comprehensive approaches that enhance the analysis and interpretation of laboratory test results to give healthcare providers the ability to make proper assessment of a patient's condition over time, reducing the occurrence of adverse outcomes.

At the same time, researchers on the healthcare engineering arena have to be aware that the use of complicated techniques to analyze this big spectrum of data could complicate the proper interpretation of the outcomes by the physician. All the decision support tools have to be designed with the objective of being interpretable for any physician in order to make it easily transferable to any clinic and to improve medical decision on healthcare settings.

All these issues open a broad research field where there are numerous opportunities for researches across a variety of disciplines for help healthcare providers to improve patient care. In the next section it is described research opportunities that the author explored on this dissertation.

1.1.2 Research Opportunities

Currently, research in healthcare engineering has become one of the most important areas to generate high societal impact due to the integration of several areas of knowledge to the service of people health improvement. A variety of multidisciplinary research endeavors have been developed lately associated to healthcare. Many of them have as their aims the development medical devices, methodologies to improve disease diagnosis processes, analysis of pandemic outbreaks, resource allocation and patient monitoring techniques, among others.

A fundamental opportunity identified by the author is in improving the effectiveness of current practices in interpreting laboratory test results, by the development of a dynamic approach that improves medical practice in monitoring postsurgical patient condition.

Patient monitoring procedures have been developed basically to follow up patient evolution during their stay in hospitalization. As mentioned before, laboratory tests become one of the more used tools to monitor the patient's health. According to the patient's condition, physicians order different sets of laboratory tests, to either confirm a hypothesis about the evolution of the patient or just as a part of a routine screening rule.

Two common tests order by physicians to perform a general screening of a patient's condition are: Complete Blood Count test (CBC) and Basic Metabolic Panel (BMP). These tests are utilized to identify abnormalities in heart rhythm and brain function, as well as common conditions such as anemia and infections [5].

Given that patients who underwent complicated surgery procedures and patients admitted in intensive care units (ICUs) represent a large proportion of the deaths in the

US [2, 3], it is critical to develop research endeavors in related to the analysis of laboratory test results to improve the monitoring process of these patient populations. Based on the indentified opportunities, the objectives that are perused on this research are stated in the next section.

1.2 Research Objectives

The overall objectives are threefold: (1) to improve the quality of medical inference based on the better interpretation of laboratory tests data, (2) to enhance the timely identification of postsurgical complications of patients who underwent cardiovascular surgery, and (3) to advance the provision of a more personalized patient care.

As a result, the author expected that practices of postsurgical patient monitoring can be enhanced by the development of this multi-test-based approach to guide medical inference. A positive impact may be achieved in improving patient outcomes, reduction in patient monitoring cost, decrease of time interpreting tests results and more effectiveness in timely identifying patient complications.

1.3 Brief Research Description

This research proposes a methodology to analyze laboratory test results of patients who underwent cardiovascular surgery, to assess their risk of complications and death during each phase of the recovery cycle. The population included on this study is composed by patients admitted at surgical intensive care unit (SICU) after undergoing coronary artery bypass, aortic value replacement and mitral valve replacement at the James A. Haley Veterans' Hospital (JAHVA), Tampa, Florida. The VA system is largest healthcare delivery network in the US and has a significant historical dataset of medical records, probably the most comprehensive in the country. In addition, the JAHVA is the

busiest facility in the VA system due to the number of active soldiers that are referred to JAHVA. This provides a tremendous opportunity to have significant national impact and potential transformed the way laboratory results are analyzed when providing medical care to patients.

The analysis considers the characterization of the behavior of commonly ordered laboratory tests to monitor patient condition during the postsurgical period. Initially, the author applied non-parametric statistics to determine differences on the behavior of these results across patients who experiences complications and patient who did not. Also, a time series of laboratory test results was constructed to first identify different laboratory result patterns and then generate patient recovery profiles over time based on the decomposition of the time series in segments that represent different stages on the patient's recovery cycle. Several mathematical and statistical techniques are used to achieve this goal, including time series clustering, data mining, fuzzy logic, among others.

1.4 Organization of the Dissertation

The remainder of this dissertation is organized as follows:

- Chapter 2 contains relevant literature review. The chapter describes current practices in interpreting laboratory test results, and the analysis of the importance of commonly ordered test in monitoring patient condition. This section also shows a description of techniques for the analysis of time series, clustering and fuzzy logic.
- Chapter 3 describes the research problem, description of the proposed approach and the identification of challenges in interpreting laboratory tests results as a dynamic function.

- Chapter 4 describes the dataset construction process as well as the design, evaluation, and validation of the proposed methodology for the analysis of laboratory tests results.
- Chapter 5 describes the performance of the proposed methodology for the analysis of laboratory test results. Also an analysis of considerations for practical use of the methodology is presented as well as guidelines for the user.
- Chapter 6 concludes the dissertation by describing the expected benefits after the implementation of the proposed methodology. It also describes possible directions for future work.

Chapter 2: Literature Review

Chapter 2 contains relevant literature review. The chapter describes current practices in interpreting laboratory test results, and the analysis of the importance of commonly ordered tests in monitoring a patient's condition. This section also shows a description of techniques for the analysis of time series, clustering and fuzzy logic.

To better understand the value of research in improving the methodologies to interpret laboratory test results, it is necessary to identify which are current practices used by physicians and the relevant work that supports it. The next sections describe relevant work and techniques that are used to interpret laboratory test results and time series data in healthcare and in other industries.

2.1 Analysis of Laboratory Test Results: Current Practice

Development of standards for the analysis of blood test indicators is based on the records from laboratories' patient population or by recruiting a group of reference subjects classified as "healthy". Reference ranges are commonly created based on results from the healthy population of an institution, including the values that correspond to the 95% ($\mu \pm 2$ standard deviations) of the results. This guideline relies on the fact that several reference ranges are proven to follow a normal distribution [6]. However, there is not an agreement on the methodology to determine these standards, resulting in method-dependent standards, and as a consequence, reference values vary across clinical laboratories [6] i.e., a survey of 525 clinical laboratories showed that the reference range

of total plasma calcium varies from 8.3 to 8.8 milligrams per deciliter as the lower limit, and from 10.2 to 10.7 milligrams per deciliter for the upper limit [7].

Methodologies to develop reference ranges are sometimes difficult to deploy due to the time needed to collect samples, cost and knowledge needed to validate the results [8]. There are two basic reference ranges: health-associated and decision based ranges [9]. Health associated ranges are based on subjects in good health condition while decision based ranges are based on limits that characterize a specific medical condition or determines an intervention.

Notice that, even for homogenous populations, the behavior of the human body differs among individuals. Existing reference ranges are used to identify abnormalities in the patients' test results without really knowing what a normal result is for a specific patient, even when historical data about laboratory results is available, presenting a challenge to healthcare providers to improve personalized healthcare delivery practices.

Unfortunately, these techniques mostly rely on the fact that single data points can be an indicator of a condition or as a decision guideline to order an intervention, ignoring what is happening to the patient over his/her cycle of care. Same laboratory test results can be an indicator of different stages on the progression of a specific disease: for example, figure 2.1 shows plasma calcium results for two patients during their postoperative recovery in ICUs.

Cases like this could be often observed in medical practice. It is important to include in the analysis of laboratory test results a temporal component that really captures what is happening over time. This will allow physicians to have a more complete patient profile

since they can compare if the result is normal according to the stage on the patient cycle of care, and not only according to the corresponding reference range.

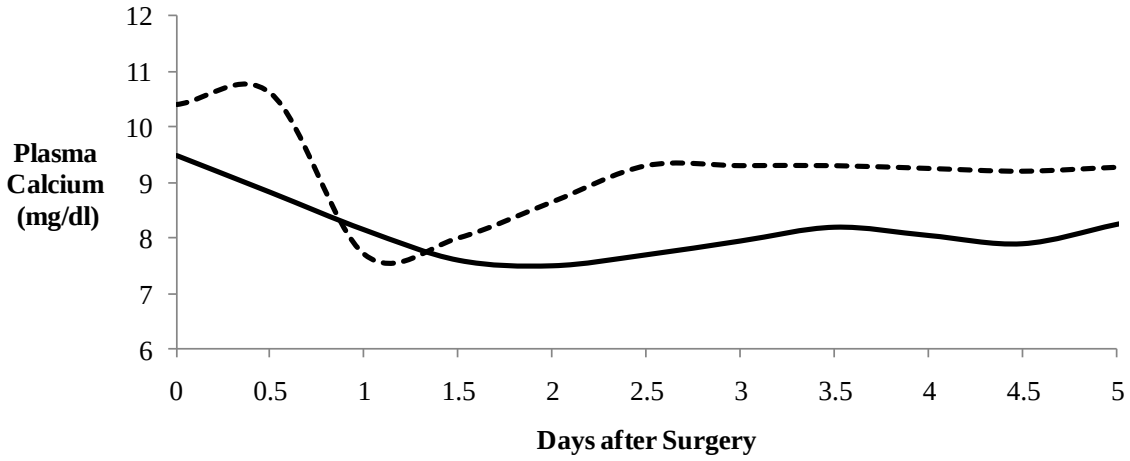

Figure 2.1 Plasma calcium results for two patients during their recovery in ICUs

2.2 Patient Monitoring Techniques

This section presents a review of relevant research associated to monitoring techniques of patients with heart disease or patients who underwent cardiovascular surgery.

Research efforts in monitoring patient condition of patients suffering heart disease reveal that four major aspects have been typically addressed: (1) understand physician's decision making process, (2) determine effective measures to assess patient health condition and (3) modeling and predicting patient outcomes (i.e. logistic regression approach) [18, 19, 20, 21, 22, 23].

There is a body of work related to the analysis of the relationship of patient demographics and the differences in patient health. However, one aspect that has been not addresses commonly is the differences in physician's decision making process that causes differences in the prescribed medicines or the disease management decisions.

Aspects like physician's education, culture or age could influence these differences. Differences iin physician's diagnosis have been studied for patients suffering coronary heart disease (CDH) [10]. In this study, the authors designed a factorial experiment to test how four indicators affected physicians' decisions regarding the diagnosis of CHD. 256 physicians were included on the study in a randomized manner. As a result, the authors found that patient's gender is one of the aspects that biased physicians' decisions. However, factors such as social class and race did not have a significant influence.

Other studies describe different factors that causes that physicians make suboptimal diagnostic and decisions about treatments [11]. The main conclusion of this study is that many of the listed biases affect, in the medical practice, how they gather and use evidence while performing diagnoses. This situation could cause deficiencies in healthcare delivery such as patient mismanagement, incorrect diagnosis and adverse outcomes. Arnold and Anderson [45] stated that it is normal that physicians, like any other person, have biases in their reasoning and the best strategy to mitigate their effect on the decision making process is to make them aware that biases are always present, so they can avoid them. As evidence of the positive effect of educating physicians about biases in medical decision making, Gruppen et al. [46] found that physicians of an institution were informed about the tendency to overestimate the likelihood of good outcomes rather than adverse outcomes.

A common bias found in the literature, documented by Bornstein [47], is the tendency of physicians to stick with a treatment even though the patient does not show any improvement. Among the reasons that may be associated to this practice are: to the

time invested on the patient, the treatment has been used for years in medical practice, and for similar patients the treatment has worked successfully.

As a consequence of biases during patient diagnosis and monitoring, the evidence-based-medicine approach has become an alternative to avoid falling on biased diagnosis [48,49]. Evidence-based-medicine is an approach that combines experiences from multidisciplinary teams and patients to perform better disease diagnosis and management [50]. By using objective information from the experiences of all clinical personnel, several sources of bias can be mitigated. One of the most important is physicians' intuition what makes them to use just some pieces of information to make inferences about a patient condition.

This issue in medical practice makes the author believe that there are commonly used "rules of thumb" that may be bias based on physicians' believes. This can be observed in current practices in interpreting laboratory test results. It is commonly assumed relationships between blood test results such as albumin and ionized calcium [51], ignoring their relationship with other indicators.

Several researches have also identified the need to determine effective measures to assess patient health condition. This process is conducted to validate a hypothesis related to the relationship of an indicator with the presence of a condition on a patient. On this matter there are standard tests (i.e. glucose level and the presence of diabetes, or platelet count and hemophilia) but rarely physicians assess patient condition by comprehensively considering multiple tests as markers of a specific condition. For patients with co-morbidities it is more complicated to perform an accurate assessment of what exactly an

indicator is showing and, even more critical and difficult to identify, in which stage of the disease is the patient [12, 13, 14, 15, 16, 17]

Analyzing laboratory test results, including their temporal variation, become a difficult task for physician due to the fact that there is a lack of techniques and tools that will help them detect changes and hidden interactions among tests results over time. Most of the work on this area analyzed patient condition using univariate measures and static data.

There is extensive literature discussing methodologies to improve patient monitoring procedures, but without simultaneously consider relevant aspects such as the effect of time, multivariate indicators of patient condition or laboratory tests history. In general, modeling patient disease progression overtime and patient monitoring can be achieved by using time series analysis. One of the most common techniques to monitor patient condition is following patient's heartbeat. Time series analysis has been utilized to determine differences between the heartbeat of healthy patients and patients with severe congestive heart failure [52], a young healthy patient population versus an elderly population [53], patients suffering from coronary artery disease with healthy patients [53], and for the characterization of patients suffering from epilepsy [54].

Time series has also used to study variations on laboratory test results, such as creatine [55]. Time series has also used to monitor routine diagnostic test data from for patients with severe influenza (AH1N1) to elaborate strategies for its control [55]. However there are not extensive studies for the analysis of laboratory tests to monitor patient condition during their hospitalization time.

Although laboratory tests are used for general screening purposes in medical practice, the characterization their tendencies overtime are not clearly stated in the literature. However, modeling disease progression has been studied for multiple sclerosis [27] and, mostly for detection of influenza pandemic outbreaks [55, 56, 57]. Although there are books and extensive literature review about methods to interpret temporal data and biostatistics [28], there are not applications related to the use of laboratory test results to monitor patient condition in ICUs.

There are other techniques, such as Markov models and functional analysis[31, 32], used to modeling disease progression [30] and screening, such as aortic aneurysm [29], severe crohn's disease [58,59], hepatitis C [60], infectious diseases [61], breast cancer [62], prostate cancer [63], among other applications.

The analysis of laboratory test results presents a challenge, due to their multivariate nature (components of CBC and BMP) and the non-standardized sampling process. Unfortunately, the test results data is not uniformly sampled due to the lack of a standardized sampling procedure. The periodicity of the sampling is determined by the physician, which complicates a direct comparison of the patients' evolution.

In other areas of knowledge, authors have done the analysis of similar data using multivariate approaches for a numerous applications with the objective of characterizing patients into clusters [24, 25, 26].

2.3 Similarities among Patients' Recovery Cycle

Several authors have applied clustering methods to find similarities among elements of a population. General clustering methods are modified to be applicable to dynamic environments (i.e. k-means, c-means, agglomerative hierarchical method) for diverse

purposes [33, 34, 35]. The variation on these methods from their original form is based on the replacement of similarity measures for static data with an expression for dynamic data [36]. Commonly used similarity measures are Euclidean distance [25, 33, 35], Pearsons' correlation coefficient [36] and Kullback-Lieber distance [35]. The objective is to maximize the sum of similarity measures between elements within a cluster [36].

Hard-partition-based [24, 34], fuzzy [33, 35, 37] and wavelet-based algorithms [38], among other techniques, are also used to create time series clusters. However, none of these techniques has shown an optimal procedure to estimate the total number of clusters [36]. It is necessary to develop an approach to efficiently capture underlying patterns of medical data that could help physicians obtain valuable information about patients' risk of complications and improve the quality of healthcare delivery.

2.4 Commonly Ordered Laboratory Tests

Laboratory tests are ordered by doctors as one of the sources to diagnose patients' diseases and as a component of health condition progression. The most common blood tests are the CBC and the BMP.

2.4.1 Complete Blood Count (CBC)

This test is compounded by a set of indicators such as red blood count, white blood count, hemoglobin, hematocrit, and platelet count. The first four indicators are the main reason to order a CBC, since they provide information to perform a general screening of patient condition.

On the other hand, platelet levels are commonly tested before surgery and during the procedure to test the ability of the human body to heal wounds and traumas generated by the surgery. Platelets are cell fragments circulating in the blood stream and involved in

the cellular mechanisms leading to the formation of blood clots. Dysfunction or low levels of platelets predispose the body to bleed. On the other hand, high levels may increase the risk of thrombosis. Treatment to control platelet count could vary among patients regarding to the severity of the disorder. It is noticed that if the detected amount of platelets is slightly higher (or lower) than the acceptable limits, the intervention would be different if the gap between those two is huge. It is necessary to develop a model to analyze these dynamics to prevent possible adverse events and improve patient care delivery.

Currently, doctors compare the results of platelets with its reference range. The reference range is an interval used by doctors to compare whether a test result is considered normal or not. Reference ranges usually consider 95% of the expected results of a healthy population within its bounds. Unfortunately, doctors just realize that the platelet count is low, or high, after the test, without having a system that helps them to identify these complications in advance. The development of techniques that allow doctors to anticipate dangerous levels of platelets will help in preventing the occurrence of adverse events.

2.4.2 Basic Metabolic Panel (BMP)

The analysis of the components of the BMP provides important information regarding fluid balance in the human body, particularly electrolytes. In general, measuring electrolytes is useful in monitoring vital normal functions such as heart rhythm and neuromuscular function [6 and 7]. Some of the known conditions related to fluid balance are muscle weakness, kidney disease, and heart disease. Specifically, calcium level is the related to bone, teeth healthiness, muscle function, nerve function and blood clotting.

Calcium is found in the human body in three forms, physically complexed in the bones, ionized (free in the blood stream) and bound to proteins, mostly plasma albumin. The level of calcium is known to be associated to the level of plasma albumin, a protein that constitutes 60% of plasma proteins [8]. The level of plasma calcium is considered normal if it falls within 8.5 - 10.5 mg/dl. Even when there is a disorder in the plasma albumin, physicians have developed an estimate of the plasma calcium, called corrected calcium [9]. This expression has been proven to be a rough estimate [10 and 11], but it is still used in practice.

Although, there is a relationship between plasma calcium and plasma albumin, changes in plasma calcium could also be influenced by the variation in ionized calcium. The ionized calcium is the metabolically active form of calcium that is available in the blood for interactions in the cells, but is not often measured in clinical use, largely by tradition. Physicians order the arterial blood gas test, mostly to check conditions such as oxygenation problems, acid-base disorders, and breathing difficulties [12]. Normal levels of ionized calcium are between 1.1-1.4 mmol/L. Ionized calcium is not altered by changes in plasma albumin, and it is generally believed that, ionized calcium is quite stable and not altered acutely, although this study will investigate whether that belief is in fact correct.

Based on preliminary observations, both plasma calcium and ionized calcium seem to manifest a noticeable and sustained decrease after cardiovascular surgery. This behavior appears to be a component of the negative acute phase response, and it appears to occur regularly in the patient cohort that underwent this type of surgery. Figure 2.2 shows the

patients' average plasma calcium and ionized calcium during the first three days after surgery, being zero the day of surgery.

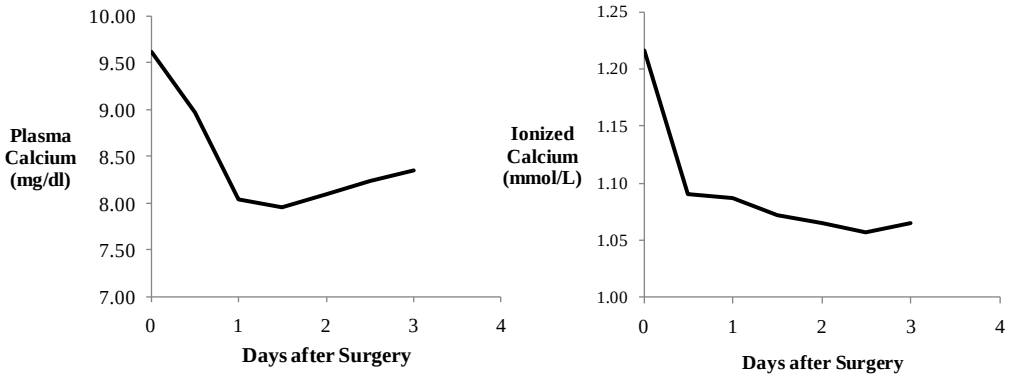

Figure 2.2 Plasma calcium and ionized calcium patterns after surgery

It is noticeable that both indicators fall dramatically after surgery, to levels that would usually be considered quite low, but without any clinical manifestations in the patients. However, if plasma calcium turns out to be a good marker of patient recovery, its behavior is expected to be different for patients who experienced complications. The next chapter presents a description of the methods used in this research to analyze the plasma calcium patters during the patients' recovery cycle.

Chapter 3: Description of the Proposed Approach to the Analysis of Postsurgical Laboratory Tests Results

The population used in this study is composed by 305 patients admitted to the SICU of the JAHVA after undergoing cardiovascular surgery. The researchers used de-identified data to conduct the study, following the requirements established by IRB, JAHVA R&D and HIPAA for such a study. The dataset contained information about patients' clinical history including date of admission, surgery type, date of surgery, date of discharge and a complete history of laboratory tests results. Accurate dates and times were required in order to establish the time series basis of the data, but all identifying information was excluded. A description of the assumptions and methods used to analyze the data are presented in the next sections.

3.1 Surgical Procedures (Interventions)

Patients who underwent cardiovascular surgery were identified using a database search based on assigned ICD-9 codes (International Classification of Diseases) [13] (see table 3.1). The ICD-9 codes provide a classification for diseases, symptoms, abnormalities and causes of a disease. This classification assigns each disease to a unique category and code. The World Health Organization (WHO) published these codes as a guideline to compare diseases and symptoms around the globe.

Twenty four cardiovascular procedures were included in this study; they are listed on table 3.1. All patients undergoing one of the identified procedures during the time period January 2006 to April 2008 were included.

Table 3.1 ICD-9 codes of the cardiovascular procedures included in the study

ICD – 9 Codes	**Bypass Procedures**
36.10	Aortocoronary bypass for heart revascularization, not otherwise specified
36.11	(Aorto)coronary bypass of one coronary artery
36.12	(Aorto)coronary bypass of two coronary arteries
36.13	(Aorto)coronary bypass of three coronary arteries
36.14	(Aorto)coronary bypass of four or more coronary arteries
36.15	Single internal mammary-coronary artery bypass
36.16	Double internal mammary-coronary artery bypass
36.17	Abdominal-coronary artery bypass
36.19	Other bypass anastomosis for heart revascularization
39.22	Aorta-subclavian-carotid bypass
39.23	Other intrathoracic vascular shunt or bypass
39.24	Aorta-renal bypass
39.25	Aorta-iliac-femoral bypass
39.26	Other intra-abdominal vascular shunt or bypass
39.28	Extracranial-intracranial (EC-IC) vascular bypass
39.29	Other (peripheral) vascular shunt or bypass
ICD - 9 Codes	**Mitral Valve Procedures**
35.02	Closed heart valvotomy, mitral valve
35.12	Open heart valvuloplasty of mitral valve without replacement
35.23	Replacement of mitral valve with tissue graft
35.24	Other replacement of mitral valve
ICD - 9 Codes	**Aortic Valve Procedures**
35.01	Closed heart valvotomy, aortic valve
35.11	Open heart valvuloplasty of aortic valve without replacement
35.21	Replacement of aortic valve with tissue graft
35.22	Other replacement of aortic valve

Initially, the surgical procedures and their corresponding dates were identified. Subsequently, the surgery dates were used as a common time reference for the analysis of the postsurgical period for each patient. Finally the surgery date for all the patients was defined as "time reference zero", delineating the beginning of the post-surgical period.

3.2 Reference Ranges

The behavior of the laboratory test results differ among individuals, even for homogeneous populations. To address this issue, physicians use reference ranges to determine if a specific test result is considered normal [14 and 15].

Reference ranges are commonly created based on results from the healthy population of an institution, including the values that correspond to 95% (mean ±2 standard deviations) of the results. This guideline relies on the fact that several reference ranges are proven to follow a normal distribution [15]. For the purpose of this study, existing reference ranges for laboratory test results are used to identify abnormalities in the test results.

There is not agreement on the appropriate methodology to determine these standards, resulting in method-dependent standards, and as a consequence, reference values vary across clinical laboratories [16] i.e. a survey of 525 clinical laboratories showed that the reference range of total plasma calcium varies from 8.3 to 8.8 milligrams per deciliter as the lower bound, and from 10.2 to 10.7 milligrams per deciliter for the upper bound [17].

The authors developed reference ranges for the actual population used in this study using historical plasma calcium data (preoperative). The most recent preoperative value is used as a baseline to reference the postoperative values.

3.3 Patient Population

The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) is "*the first nationally validated, risk-adjusted, outcomes-based program to measure and improve the quality of surgical care*" [18]. Hospitals participating in the program have access to different reports and support that help them make informed decisions and provide better healthcare delivery. As a part of this program, the JAHVA collects information about the evolution and outcomes of all patients undergoing cardiovascular surgery.

Each patient record is reviewed and abstracted by a trained surgical advanced practice nurse and the clinical information is integrated with quantitative data extracted from the hospital database. This information will be used to identify which patients, within the dataset, had postsurgical complications and which patients died after surgery. The patients included in this study are classified in four groups according to their recovery cycle and their outcome at the end of the cycle of care. The four patient types are listed below:

- *Type 1*. Patients who had a satisfactory recovery process and were discharged without any identified complication.
- *Type 2*. Patients who survived the perioperative period, had complications during the recovery process, but survived and were discharged from the hospital.
- *Type 3*. Patients who survived the perioperative period, had complications and then died within 30 days after surgery.
- *Type 4*. Patients who died during the initial postoperative period (within 4 days after surgery)

- *Excluded*. Patients who died intraoperatively were excluded from the study as there were no data available for analysis.

In the study patients who survived to day 30, but then died at a later date (typically post-discharge), are not considered as deaths, since they are typically associated a new, intercurrent event not present during the period of study. Examples of postsurgical plasma calcium test results for these four groups of patients are shown in figures 3.1 a, 3.1 b, 3.1 c and 3.1 d:

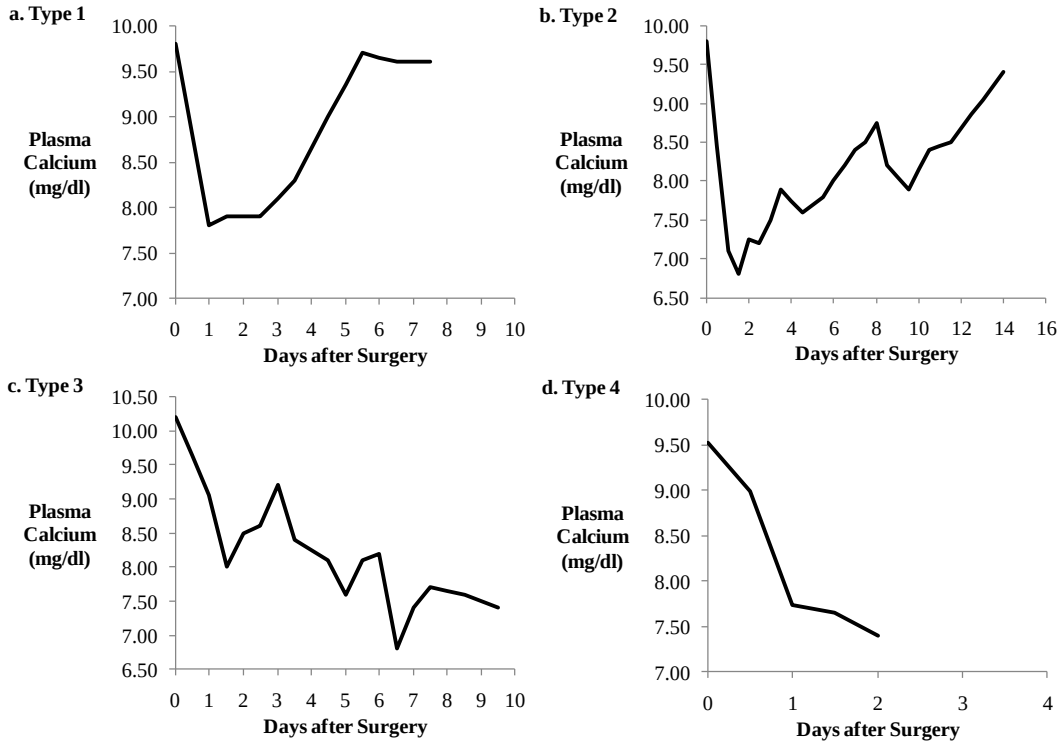

Figure 3.1 Examples of postsurgical plasma calcium for all patient types

According to surgeons at the JAHVA, patients who had a satisfactory recovery cycle are expected to be sent home approximately within 7 days after surgery. As it can be observed in figure 3.1 a, patients had a fall in plasma calcium, below the lower bound of

the reference range, reaching its minimum approximately during the second day after surgery. Then, the plasma calcium starts to go back to levels within the reference range until it reaches levels near to the baseline. The time of recovery is longer for patients who experienced complications. This is also reflected in the time required for plasma calcium levels to return to normal levels. For these patients (figure 3.1 b) the continuous decrease in the level of plasma calcium reflects the lack of stabilization on patient condition. Type 3 patients (figure 3.1 c) had an initial increase in calcium level, but after a few days the plasma calcium fell. On the other hand, patients who died during the initial postoperative period show no recovery after the natural drop in plasma calcium.

In general the analysis of the patterns of laboratory tests results over time could provide physicians with valuable information to assess patient recovery and anticipate possible complications on patient condition. In the next section an approach to further analyze laboratory test result patterns is presented.

3.4 Analysis and Characterization of Laboratory Test Results over Time

Several laboratory test results have a negative acute response to the surgery. Physicians in the JAHVA have identified that other test results present an acute response after surgery (e.g. platelet count). For a normal patient, these indicators fall until reaching a minimum, commonly below the lower bound of the reference range, and then begin to recover normal levels.

In the case of plasma calcium, the minimum level is 7.734 mg / dl (mean value for the population considered in this study), and then begins to recover its normal levels. The time to return back to values within the reference range could vary among patients, due to the differences in the recovery cycle. As a reference, the plasma calcium recovery

cycle during the postsurgical period as well as some notations, are described as follows (figure 3.2):

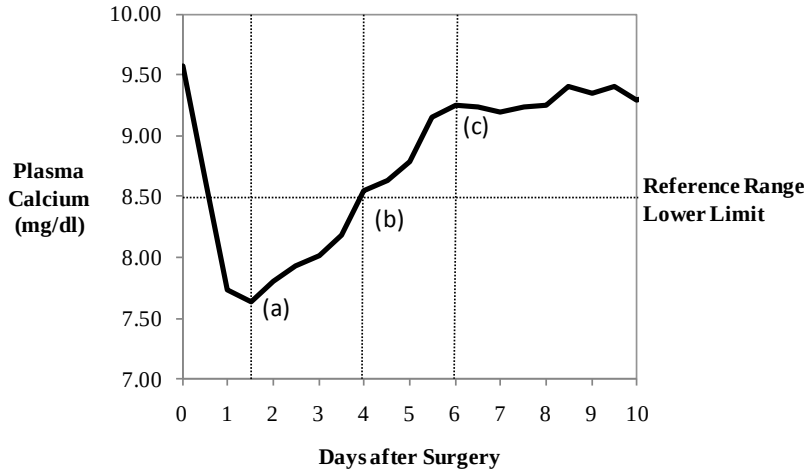

Figure 3.2 Plasma calcium recovery cycle

- *Drop Phase (DP):* the time-span immediately after surgery when the patient's test result level drops significantly until it shows a change in the decreasing trend. The drop phase length is the time between surgery and the initial minimum (a).
- *Recovery Phase (RP):* the time-span from the initial minimum (a), until the time when the results reach normal levels. This phase can be further characterized: from the initial minimum (a) until the test results reach the lower bound of the reference range (b) and from the initial minimum (a) until return to the baseline (c).
- $R_{DP\text{-}min}$*:* Minimum result (R) at the end of the drop phase.
- $R_{G\text{-}min}$*:* Global minimum test result. For patients with a satisfactory recovery.

For example $Ca_{DP\text{-}min}$ and $ICa_{DP\text{-}min}$ represent the minimum plasma calcium and ionized calcium at the end of the drop phase. On the other hand, $Ca_{G\text{-}min}$ and $ICa_{G\text{-}min}$ are the global minimums.

- $T\text{-}R_{G\text{-}min}$: Time after surgery corresponding to $R_{G\text{-}min}$
- $T\text{-}R_{DP\text{-}min}$: Time after surgery corresponding to $R_{DP\text{-}min.}$ In many patients, presumably uncomplicated, $T\text{-}Ca_{G\text{-}min}$ and $T\text{-}Ca_{DP\text{-}min}$ are expected to be the same.

Various characteristics of the patient's recovery are analyzed. Since several of them do not follow a normal distribution, non-parametric tests are performed to show the relationship among these features and the patient's recovery.

3.5 Identification of Postsurgical Complications Based on Test Results

Research focusing in data driven models to support medical decisions has increased in the last years [39]. One of the aims of research in this field is to create enhanced patient profiles that consider available medical information to improve the decision making process. However, the complex nature of laboratory test results, may lead to overlook patterns associated to patients who experienced postsurgical complications. This may happen because some of these patterns are undetectable to the naked eye, and to lack of robust techniques to conduct medical inference. Thus it is important to investigate if additional valuable information can be extracted from the CBC and BMP components that will help to determine the likelihood of a patient suffering postsurgical complications.

A CBC test is ordered to monitor disease progression, response to treatment or just as a routine checkup [5]. A CBC test helps physicians to start investigating causes of symptoms suffered by the patient, such as weakness, fatigue or pain [5]. Common identifiable conditions based on a CBC test are anemia, infections and leukemia [6]. Atypical variations on the CBC results may lead to further investigate the underlying medical condition that caused such symptoms. A CBC includes information about

hemoglobin (Hbg), white cell count (WBC), white cell differential count, red blood count (RBC), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count, and mean platelet volume (MPV) [4]. When ordering this test physicians are mostly interested in Hbg, WBC and RBC due to their known relationship with most common diseases [5, 6, 40]. Thus physicians use the test is to validate their hypothesis about the condition that the patient is suffering. Physicians working with the research team strongly argue that the concurrent analysis of other results could improve the assessment of the patient condition.

Similarly, BMP test is commonly ordered to assess patient condition. BMP measures blood sugar levels, fluids balance, and kidney function [40], in terms of the levels of sodium, potassium, creatinine, total bilirubin, total protein, carbon dioxide, glucose, chloride, blood urea nitrogen (BUN) and calcium. Blood sugar levels are measured in terms of glucose, which is the most important source of energy used by the human body. Fluids balance is measured in terms of electrolytes (potassium, calcium and sodium), needed to keep normal live functions, such as heart rhythm, muscle contraction, and brain function [6]. Health conditions associated to electrolytes unbalance are heart disease, muscle weakness, kidney disease, endocrine diseases, eating disorders, or bone disorders. There are conditions that affect fluids balance, such as diarrhea, vomiting, fever, or taking diuretics. Also, calcium levels are important for healthy bones and teeth, as well as for normal muscle and nerve function.

It becomes necessary for physicians to enhance their ability to interpret laboratory test results, to timely identify changes in a patient's condition, order accurate interventions

and make better patient care decisions. The fundamental goal is to improve the current use of laboratory results by demonstrating how to extract valuable information from existing clinical datasets.

Laboratory tests are ordered by physicians as part of a discrete monitoring process of patient health evolution. As mentioned before, CBC and BMP are the most common tests ordered by physicians to assess kidney functions, electrolytes and blood cells count. R_i denotes a series of l laboratory results $\{k=1, \ldots, l\}$, for a given patient i $\{i=1, \ldots, n\}$, for a set of m tests $\{j=1, \ldots, m\}$ can be represented as follows:

$$R_i = \begin{bmatrix} r_{i11} & r_{i12} & \ldots & r_{i1k} & \cdots & r_{i1l} \\ r_{i21} & r_{i22} & \cdots & r_{i2k} & \cdots & r_{i2l} \\ \vdots & \vdots & \ddots & \vdots & \cdots & \vdots \\ r_{ij1} & r_{ij1} & \cdots & r_{ijk} & \cdots & r_{ijl} \\ \vdots & \vdots & \cdots & \vdots & \cdots & \vdots \\ r_{im1} & r_{im2} & \cdots & r_{imk} & \cdots & r_{iml} \end{bmatrix} \qquad (3.1)$$

In real practice, laboratory tests are ordered by the physicians without following a standard guideline about its periodicity. Moreover, there are no methodologies available to determine an appropriate sampling rate for monitoring patients after undergoing cardiovascular surgery. This creates a non-uniformly sampled process and a problem if a physician wants to compare the recovery of two patients at the same time.

For a given patient i and test j, the vector R_{ij} represents the history of laboratory test results over time and r_{ijkt_k} the k^{th} result, sampled at time t $\{t=t_1, \ldots, t_k\}$.

$$R_{ij} = \left[r_{ij1t_1}, r_{ij2t_2}, \ldots, r_{ijkt_k}, \ldots, r_{ijlt_k}\right] \qquad (3.2)$$

Notice that the values of k denote the order in which the samples are taken. On the other hand, t represents the actual time when the sample was taken. Since we want to

analyze patients' recovery cycle, time zero will be assumed as the time of surgery for each patient.

For a non-uniformly sampled process, two patients may not have the same number of samples, and they may not be taken at the same intervals. Moreover, depending on the patient's evolution, the length of stay will also vary among patients, increasing the numbers of samples. Non-uniformly sampled data creates a challenge for various methods of analysis, such as time series, due to the need of converting these irregular observations to periodic observations [36]. To construct standardized datasets, the proponents will test the ability of several interpolation and modeling techniques to capture the changes in the components of CBC and BMP over time. Once the best technique is identified, the proponents will construct an equally time-spaced sequence of test results for every patient.

Due to the trauma caused by the surgery, the loss of blood and the effort of the human body to keep normal functions, a major disturbance is created in the patients' test results after surgery. Two patterns are observed in test results immediately after surgery: positive and negative acute response to the surgery. As the names suggest, a variable shows a negative/positive acute response when its levels drop/increase significantly after an event, in this case surgery. Physicians working with the research team have observed that the calcium level falls until it reaches an average level of 7.5 mg / Dl (reference range = [9, 10.5] mg/Dl), and then it begins to recover its normal levels after the second day of the postsurgical period. The time to return back to the reference range could vary among patients, due to the differences in the recovery cycle.

3.6 Characterization of the Time Series

Based on the aforementioned classification, an analysis of the differences of the patterns of the *DP*, *RP*, $R_{DP\text{-}min}$, $R_{G\text{-}min}$, $T\text{-}R_{G\text{-}min,}$ $T\text{-}R_{DP\text{-}min}$ for all patient types and laboratory tests will be performed. This analysis will provide overall statistics about the patient population. Parametric and non-parametric tests, as well as correlation analysis were performed on the data to identify differences among patients' laboratory test results and patterns among patients who had postsurgical complications.

Current patient monitoring practices rely on the power of reference ranges in detecting abnormalities in test results. Unfortunately, results are analyzed individually or at most comparing two or three tests at the same time. Physicians do not have a proper way of including more results (variables) to make inferences about the patient's condition. The proponents will identify the most relevant test results patterns associated to patients experiencing complications. Also, interpretation of suspicious patterns in test results will allow providers to improve current patient monitoring practices. The development of multi-test-based monitoring process will assist physicians to observe and understand interactions among test results and their relationship with patient's health evolution.

Healthcare information systems collect a great deal of data over time about patient evolution. As stated before, this data needs to be analyzed to provide physicians with useful information that enhance the diagnosis process. The understanding of the patient evolution during the postsurgical period would help physicians to anticipate undesirable changes in the patient's condition and prescribe treatment(s) more effectively. For example, if two patients share the same result at some point in time, physicians cannot

assure that the patients are in the same stage of their evolution after surgery. Certainly, physicians use additional data to assess patient condition (symptoms described by the patient, family history, demographics, etc.) but for patients with similar profile the evolution may vary significantly.

Patient recovery patterns vary according to the patient's health condition. Preliminary observations show that patients experiencing complications spend more time recovering normal levels (within the reference range) of platelets, calcium and mean platelet volume. The construction of a patients' similarity matrix, will provide a metric of the differences among patients' recovery.

Since all the tests results are in different scales, a time series of their rate of change will be used to construct the patients' similarity matrix. Given two consecutive test results r_{t-a} and r_t at time *t-a* and *t,* the rate of change at time *t* for a given test, q_t, can be represented mathematically as follows:

$$q_t = \frac{r_t - r_{t-a}}{a} \tag{3.3}$$

$$Q = [q_1, q_2, \dots, q_t, \dots, q_k] \tag{3.4}$$

Time series constructed based on the rate of change have different lengths due to the non-uniformly sampled nature of monitoring process. Commonly used similarity measures, such as Euclidean distance, do not consider uneven time series. However, there are methods such as dynamic time warping (DTW) that allows the calculation of distances between time series with different length. DTW will be used to calculate similarity among the patients' recovery. Let Q_i and Q_i' be the rate of change time series of tests results of two different patients: $Q_i = [q_1, q_2, \dots, q_t, \dots, q_k]$ and $Q_i' = [q'_1, q'_2, \dots, q'_{t'}, \dots, q'_{k'}]$. The DTW algorithm will compare them by lining them up to

minimize their difference. As a result, the algorithm will provide a *k x k'* distance matrix, D_{ij}, where the $D_{ij}(t,t')$ position represents the Euclidean distance between the t^{th} and the t'^{th} element of the series Q_i and Q_i' respectively for patient i and i' , and test j. The calculation of the D_{ij} matrix elements will be performed for all the components of the CBC and BMP for every patient.

The minimum distance between these time series is the sum of the elements of the warping path *W*, where:

$$W = [w_1, w_2, \dots, w_p, \dots, w_P] \tag{3.5}$$

$$max\,(k, k') \leq\ P \leq k + k' - 1 \tag{3.6}$$

The warping path *W*, is the minimum path from the position $D_{ij}(1,1)$ to $D_{ij}\ (k,k')$. The minimum path will be determined using dynamic programming techniques. The mathematical expression that represents the minimum distance between these time series is:

$$d^{j}_{Q_i,Q_{i'}} = min\frac{\sum_{p=1}^{P} w_p}{P} \tag{3.7}$$

This calculation will be performed for each pair of rate of change time series, for each pair of patients. As a result, *m*-matrices will be created for each patient, one for each analyzed test.

The *n x n* matrix *S*, shows the patients' similarity values, as follows:

$$S = \begin{bmatrix} s_{11} & s_{12} & \dots & s_{1i'} & \cdots & s_{1n} \\ s_{21} & s_{22} & \cdots & s_{2i'} & \cdots & s_{11} \\ \vdots & \vdots & \ddots & \vdots & \cdots & \vdots \\ s_{i1} & s_{i2} & \cdots & s_{ii'} & \cdots & s_{in} \\ \vdots & \vdots & \cdots & \vdots & \cdots & \vdots \\ s_{n1} & s_{n2} & \cdots & s_{ni'} & \cdots & s_{nn} \end{bmatrix} \tag{3.8}$$

where $s_{ii'} = \sum_{j=1}^{m} d^{j}_{Q_i,Q_{i'}}$. This matrix summarizes the metrics used for comparison between every two patients in the training set.

Several clustering techniques are tested to identify which one offers better performance in clustering patients' based on the matrix S. Also, the authors investigate what is the best number of clusters that better describe patient's evolution. The main focus is fuzzy clustering techniques because they could provide more detailed information about the patient condition, by providing membership values for a patient into different clusters. Other techniques are also tested.

Fuzzy clustering techniques are used on this research to efficiently cluster patients according to their similarities during the postsurgical period. It is expected that each one of the clusters will represent a specific patient recovery pattern. Let u_{iv} represent the membership value of patient *i* in cluster *v*, where *C* is the total number of clusters. The algorithm intends to minimize the expression:

$$\sum_{v=1}^{C} \frac{\sum_{i,i'=1}^{n} u_{iv}^2 u_{i'v}^2 S(i,i')}{2\sum_{i'=1}^{n} u_{i'v}^2} \qquad (3.9)$$

Membership values should satisfy the following conditions: $u_{iv} \in [0,1]\ \forall\, i, v$; $\sum_{i=1}^{n} u_{iv} = 1\ \ \forall\, v$ and, $0 < \sum_{v=1}^{c} u_{iv} < n\ \ \forall\, v$.

Next section shows an analysis of postsurgical plasma calcium, ionized calcium and platelet count based on their characterization as time series, as well as their relation during patients' recovery phase.

Chapter 4: Analysis of Postsurgical Plasma Calcium, Ionized Calcium and Platelet Count Test Results

This chapter presents an analysis of different features of postsurgical plasma calcium. The main objectives are to characterize the behavior of postsurgical plasma calcium test results and to find key differences on the plasma calcium results over time for the different patient types.

4.1 Plasma Calcium: Reference Ranges

According to the USMLE [19] the reference range for plasma calcium is between 8.5 and 10.5 mg/dl. However, since the actual baseline data is available, reference ranges for the population of this study are developed. The test results used to construct the reference ranges are the last result before undergoing surgery. Figure 4.1 shows the frequency distribution of the pre-surgical plasma calcium for the patient population included in the study. The reference range for the population of this study is [8.68 - 10.55] mg/dl (μ=9.617; σ = 0.4675). The frequency distributions found in the literature do not differ appreciably from the results obtained by constructing a reference range for plasma calcium for the population of this study (reference ranges are constructed based on the mean of the results from a healthy population ± 2 standard deviations).

Although, the plasma calcium frequency distribution shows a fairly Gaussian shape, the hypothesis of normality was rejected after performing a Kolmogorov-Smirnov test (p-value=0.034); probably due to presence of some outliers that create a heavy tailed frequency distribution. Yet a statistical test without the outliers yielded the same results although with a more symmetrical distribution. Although small subgroups (types 3 and 4) were not different by Wilcoxon test, we will assume that the parent distribution is not normal and will employ non-parametric statistical methods where applicable.

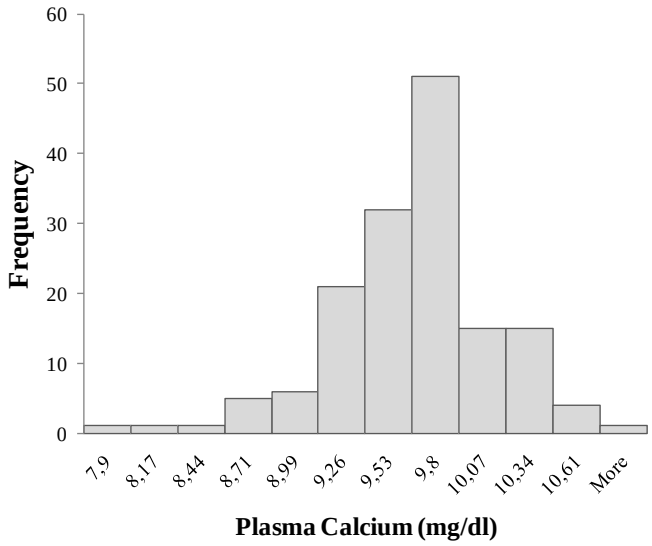

Figure 4.1 Frequency distribution of pre-surgical plasma calcium of the study population

To confirm that there were not baseline differences in the subsequently identified patient groups, the four groups were compared by a Kruskal-Wallis test, which showed no baseline difference. This was further analyzed by applying individual Wilcoxon tests between pairs of groups as a “post-hoc” test, and again there was no consistent difference between baseline groups. A summary of the results is presented in table 4.1 and 4.2.

Table 4.1 Mean and standard deviation of pre-surgical plasma calcium (mg/dl)

	Population	*Type 1*	*Type 2*	*Type 3*	*Type 4*
Mean	*9.617*	*9.685*	*9.550*	*9.794*	*9.520*
Standard Deviation	*0.467*	*0.467*	*0.462*	*0.410*	*0.427*

Table 4.2 p-values from a two-sample Wilcoxon rank sum test for pre-surgical plasma calcium

Patient Type	*P-Values*
Type 1 - Type 2	*0.010*
Type 1 - Type 3	*0.545*
Type 1 - Type 4	*0.432*
Type 2 - Type 3	*0.210*
Type 2 - Type 4	*0.901*
Type 3 - Type 4	*0.347*

It is also noted that although the *p-value* obtained by comparing pre-surgical plasma calcium for patient types 1 and 2 is equal to 0.01, the difference in the means is not significant from the medical perspective, since these values are close to the central point of the reference range. In summary the pre-surgical plasma calcium results do not provide enough information to assess how likely the patient is to have, or not, postsurgical complications.

4.2 Plasma Calcium: Initial and Global Minimums

A decrease in plasma calcium levels was initially described in a study of patients with pancreatitis; where it was found that low calcium is an indicator of a severe disease [20]. Also a decrease in plasma calcium has been reported in patients with sepsis [21]. In their long medical and healthcare practice two of the committee members, Drs. Fabri and Foulis, they have observed that a drop in the plasma calcium after cardiovascular surgery is expected as a negative acute response to the surgery.

In this study, the plasma calcium drops below the lower bound of the reference range for the majority of the patients reaching its minimum value $Ca_{DP\text{-}min}$, on average, during

the second day after surgery. Once $Ca_{DP\text{-}min}$ is reached, the plasma calcium begins to return towards a normal level for patients who had a satisfactory recovery, while for patients experiencing complications the plasma calcium does not show a stable increasing trend. For patients experiencing complications, the plasma calcium shows an initial increase towards normal levels, and then it shows a non-stable trend. In some cases, these variations make the plasma calcium results to drop even below the $Ca_{DP\text{-}min}$.

This global minimum, $Ca_{G\text{-}min}$, is expected to be the same as $Ca_{DP\text{-}min}$, for patient's type 1 and 4. For patients' type 4, who died without experiencing any increase after the initial minimum, the minimum plasma calcium is taken from the last test prior to death. Table 4.3 presents a summary of the average values for $Ca_{DP\text{-}min}$ and $Ca_{G\text{-}min}$.

Table 4.3 Mean and standard deviation for $Ca_{DP\text{-}min}$ and $Ca_{G\text{-}min}$ (mg/dl)

		Population	*Type 1*	*Type 2*	*Type 3*	*Type 4*
$Ca_{DP\text{-}min}$	*Mean*	*7.608*	*7.646*	*7.582*	*7.540*	*7.380*
	Standard Deviation	*0.587*	*0.598*	*0.579*	*0.416*	*0.726*
$Ca_{G\text{-}min}$	*Mean*	*7.549*	*7.608*	*7.513*	*7.100*	*7.380*
	Standard Deviation	*0.545*	*0.557*	*0.525*	*0.424*	*0.726*

The values of $Ca_{G\text{-}min}$ for patients type 3 and 4 are lower than for patients type 1 and 2. These values represent values reported prior to death for the majority of the patients, and differ significantly from the $Ca_{DP\text{-}\min.}$ Figure 4.2 and 4.3 show the frequency distribution of $Ca_{G\text{-}min}$ and $Ca_{DP\text{-}min}$ respectively.

Both frequency distributions show a Gaussian shape, but the normality assumption was also rejected (pvalue=0.04). A two-sample Wilcoxon rank sum test was performed to determine if there is a significant difference between the $Ca_{G\text{-}min}$ and $Ca_{DP\text{-}min}$ for all patient types (table 4.4).

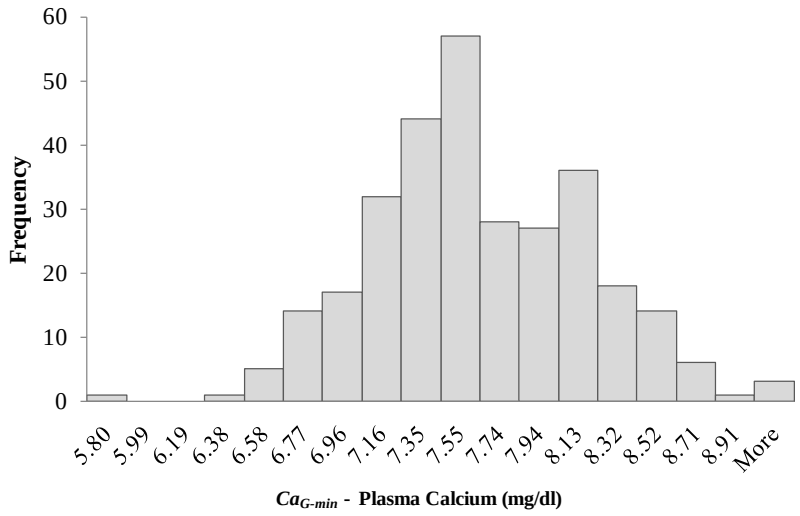

Figure 4.2 Frequency distribution of $Ca_{G\text{-}min}$

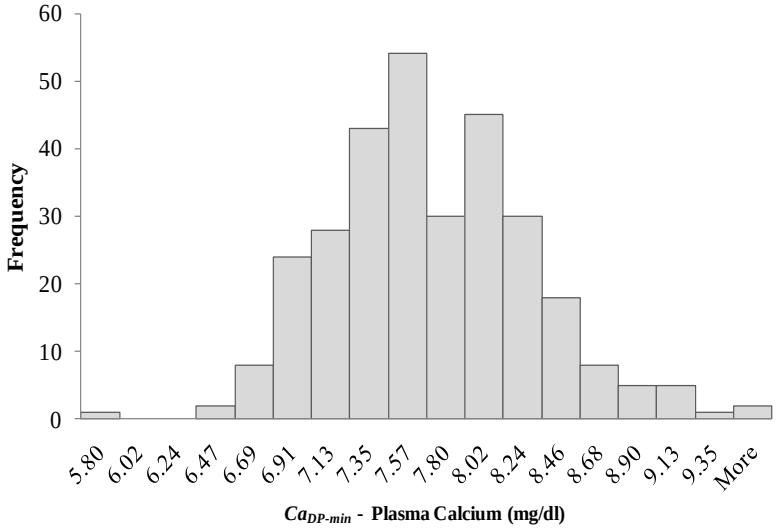

Figure 4.3 Frequency distribution of $Ca_{DP\text{-}min}$

The test results showed no significant difference in the values of minimum values of $Ca_{G\text{-}min}$ and $Ca_{DP\text{-}min}$. This implies that a single value of plasma calcium is not enough to establish whether a patient is suffering complications or not. However, a single markedly decreased level is suggestive of complications, which may signify that temporal analysis of calcium levels could provide more information.

Table 4.4 p-values from a two-sample Wilcoxon rank sum test of $Ca_{G\text{-}min}$ and $Ca_{DP\text{-}min}$

	p-values	
Patient Type	$Ca_{G\text{-}min}$	$Ca_{DP\text{-}min}$
Type 1 - Type 2	*0.372*	*0.156*
Type 1 - Type 3	*0.844*	*0.053*
Type 1 - Type 4	*0.204*	*0.236*
Type 2 - Type 3	*0.881*	*0.094*
Type 2 - Type 4	*0.277*	*0.349*
Type 3 - Type 4	*0.396*	*0.750*

4.3 Plasma Calcium: $T\text{-}Ca_{G\text{-}min}$ and $T\text{-}Ca_{DP\text{-}min}$

The time to reach the $Ca_{DP\text{-}min}$ ($T\text{-}Ca_{DP\text{-}min}$), could be an important predictor of the appearance of complications after surgery. Small values of $T\text{-}Ca_{DP\text{-}min}$ can be caused by the steepness on the drop of plasma calcium, whereas larger values could indicate a smaller effect of the surgery on the level of plasma calcium for those patients. The $T\text{-}Ca_{G\text{-}min}$ should differ among patient's groups due to the late appearance of complications for patients' type 2 and 3 during the recovery phase. It is expected that $T\text{-}Ca_{G\text{-}min}$ for these patients will be considerably larger than their $T\text{-}Ca_{DP\text{-}min}$. Table 4.5, figure 4.4 and figure 4.5 and show the behavior of $T\text{-}Ca_{DP\text{-}min}$ and $T\text{-}Ca_{G\text{-}min}$.

Table 4.5 Mean and standard deviation for $T\text{-}Ca_{DP\text{-}min}$ and $T\text{-}Ca_{G\text{-}min}$

		Population	*Type 1*	*Type 2*	*Type 3*	*Type 4*
$T\text{-}Ca_{DP\text{-}min}$	*Mean*	*1.120*	*1.033*	*1.215*	*0.952*	*0.880*
	Standard Deviation	*0.529*	*0.472*	*0.574*	*0.209*	*0.396*
$T\text{-}Ca_{G\text{-}min}$	*Mean*	*1.774*	*1.296*	*2.122*	*5.729*	*0.880*
	Standard Deviation	*2.013*	*1.095*	*2.353*	*4.807*	*0.396*

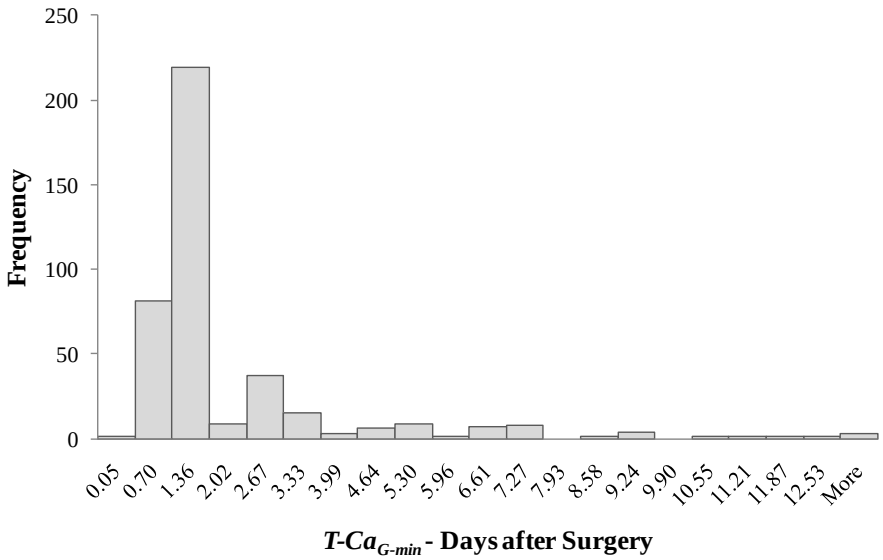

Figure 4.4 Frequency distribution of *T-Ca*$_{G\text{-}min}$

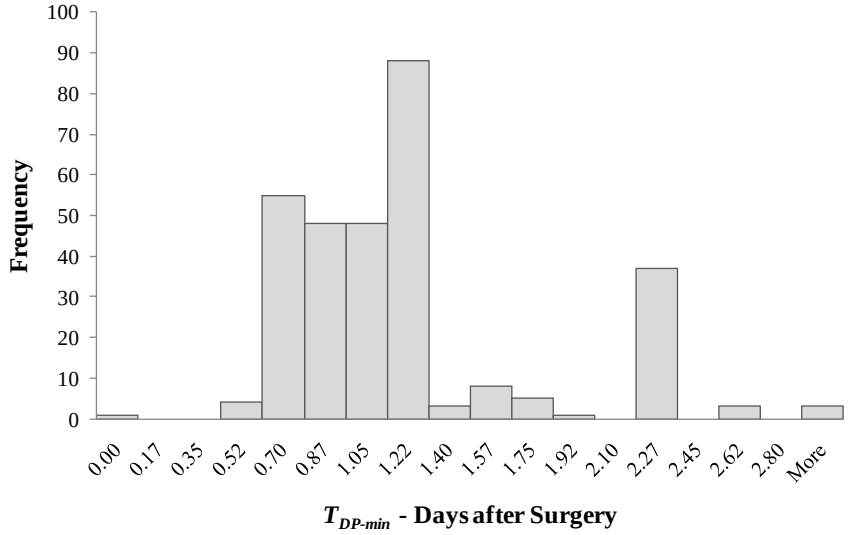

Figure 4.5 Frequency distribution of *T-Ca*$_{DP\text{-}min}$

The mean values for *T-Ca*$_{DP\text{-}min}$ show that the end of the drop phase occurs, on average, at the beginning of the second day. The means among patient groups differ just by a few hours, indicating that there is not a marked difference in the values of *T-Ca*$_{DP\text{-}min}$. However, the values of *T-Ca*$_{G\text{-}min}$ show a considerable difference among them. For patients who experienced complications and died, the value of *T-Ca*$_{G\text{-}min}$ is, on average, 5.729 days, while for patients who had a satisfactory recovery *T-Ca*$_{G\text{-}min}$ is 1.296 days. A

two-sample Wilcoxon rank sum test was performed to test the differences among the $T\text{-}Ca_{DP\text{-}min}$ for all patient types. The same analysis was carried out for $T\text{-}Ca_{G\text{-}min}$. Results are summarized in table 4.6.

Table 4.6 p-values from a two-sample Wilcoxon rank sum test of $T\text{-}Ca_{G\text{-}min}$ and $T\text{-}Ca_{DP\text{-}min}$

	p-values	
Patient Type	*T-Ca $_{G\text{-}min}$*	*T-Ca $_{DP\text{-}min}$*
Type 1 - Type 2	*0.002*	*0.007*
Type 1 - Type 3	*0.044*	*0.853*
Type 1 - Type 4	*0.313*	*0.384*
Type 2 - Type 3	*0.117*	*0.360*
Type 2 - Type 4	*0.088*	*0.133*
Type 3 - Type 4	*0.095*	*0.296*

In general there is not a significant difference in the value of $T\text{-}Ca_{DP\text{-}min}$ among patients, indicating that all the patients experience the same drop in plasma calcium after cardiovascular surgery. However, there is a significant difference in the values of $T\text{-}Ca_{G\text{-}min}$ among patients who experienced complications, type 2 and 3, and patients who did not. Patients who experienced complications have larger variability than type 1 patients during the recovery process. For patients experiencing complications, the plasma calcium drops even below the $Ca_{DP\text{-}min.}$.

The analysis of the variation of plasma calcium provides valuable information to assess patient condition. Physicians can monitor the plasma calcium based on its variation over time, having as reference the lowest level and the instance when it occurred. A negative trend of plasma calcium should trigger an alarm, indicating that there is a risk of dropping to levels close to the $Ca_{DP\text{-}min}$. The next section presents an

analysis of the variation of plasma calcium over time. This analysis is based on plasma calcium slopes during the drop and recovery phase.

4.4 Plasma Calcium Slopes during the Drop and Recovery Phase

The analysis of the variation of plasma calcium could help in the timely identification of postsurgical complications. It is necessary to analyze the temporal variation of calcium to determine what information can be extracted.

The temporal variation of plasma calcium is analyzed in terms of the slope during the drop and recovery phase. Table 4.7 shows the mean and standard deviation of the plasma calcium slopes during the drop and recovery phase for the population of this study. A two-sample Wilcoxon rank sum test was performed to test the difference of the plasma calcium slope during the drop and recovery phase for all patient types.

Table 4.7 Plasma calcium slopes during the drop and recovery phase

		Slope Drop Phase	*Slope T-Ca $_{DP\text{-}min}$ - 7th Day*
Population	*Mean*	*-2.288*	*0.178*
	Std. Dev.	*1.340*	*0.195*
Type 1	*Mean*	*-2.415*	*0.207*
	Std. Dev.	*1.291*	*0.188*
Type 2	*Mean*	*-2.144*	*0.158*
	Std. Dev.	*1.389*	*0.196*
Type 3	*Mean*	*-2.523*	*-0.033*
	Std. Dev.	*0.783*	*0.182*
Type 4	*Mean*	*-2.784*	-
	Std. Dev.	*1.433*	-

As it was shown in the previous section, the behavior of the plasma calcium (slope) during the drop phase is the same for all patients. However, there is a significant difference in the values of slope during the recovery phase (table 4.8). Notice that the

comparisons were made between type 1, 2 and 3, since type 4 patients died during the drop phase.

Table 4.8 p-values from a two-sample Wilcoxon rank sum test of the plasma calcium slope during the drop and recovery phase for all patient types

	p-values	
Patient Type	*Slope Drop Phase*	*Slope T-Ca $_{DP\text{-}min}$ - 7th Day*
Type 1 - Type 2	*0.0577*	*0.017*
Type 1 - Type 3	*0.6789*	*0.0105*
Type 1 - Type 4	*0.5452*	-
Type 2 - Type 3	*0.2825*	*0.044*
Type 2 - Type 4	*0.2482*	-
Type 3 - Type 4	*0.8345*	-

The recovery pattern of plasma calcium, following the initial minimum, appears to be a useful indicator for assessing patient recovery. Since there is not a marked difference among patients during the drop phase, differences in patient condition start to be recognized after the plasma calcium reaches the $Ca_{DP\text{-}min}$. Variations on the ascending trend of plasma calcium during the recovery phase should be an indicator of an unrecognized complication on patient condition. This is even more critical if the test results are close to the lower bound of the reference range or to the $Ca_{DP\text{-}min}$.

However, it could be argued that variations in plasma calcium are due to the variations on plasma albumin, as it is commonly assumed. The next section presents an analysis of the relationship of the variations on plasma calcium and ionized calcium.

4.5 Analysis of Ionized Calcium Results

The main objective of analyzing postsurgical ionized calcium, and its relationship with variations in plasma calcium, is to demonstrate that variations in plasma calcium are not principally due to a change in plasma albumin, but rather a proportional decrease in

ionized calcium. Since the ionized calcium is mostly sampled during the perioperative period, the analysis that is presented in next sections is based on its variations during the drop phase, which is when the major changes in plasma calcium occur

4.5.1 Ionized Calcium: Reference Ranges

On average, the pre-surgical ionized calcium is 1.169 mmol/L, which falls within the reference range which is [1.1, 1.4] mmol/L [22]. An ionized calcium reference range for the population of this study was developed based on the last result before undergoing surgery. The developed reference range is [0.955, 1.382] mmol/L ($\mu = 1.169$; $\sigma = 0.107$).

The upper bounds of the reference ranges found in the literature do not differ significantly from the results obtained by constructing this reference range for ionized calcium (mean + 2σ), but the lower bound is considered low for this population. Approximately, 16% of the patients have levels of ionized calcium below the lower bound of the reference range prior to surgery. Figure 4.6 shows the frequency distribution of the pre-surgical ionized calcium.

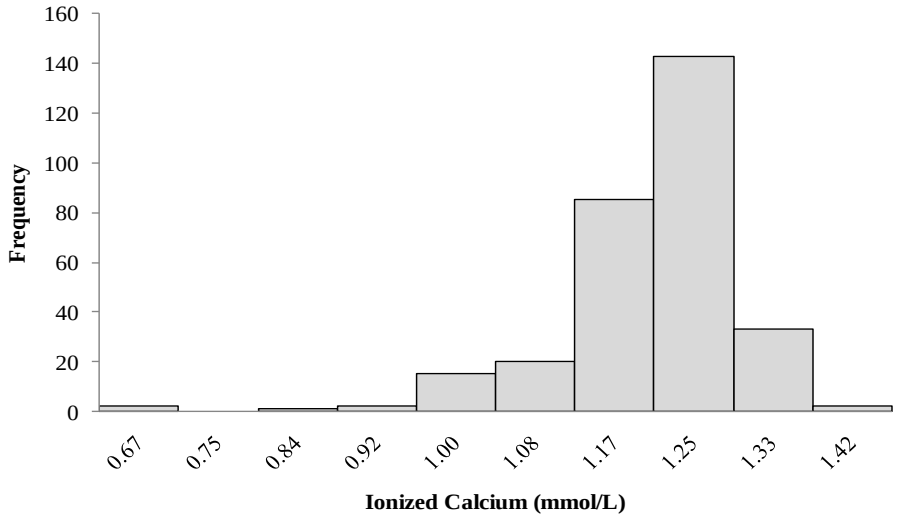

Figure 4.6 Frequency distribution of pre-surgical ionized calcium of the study population

The pre-surgical ionized calcium for all the patient types appears to be similar. Table 4.9 shows the mean and standard deviation of pre-surgical ionized calcium by patient type. Since the assumption of normality was rejected (*p-value* =0.018), a Kruskal-Wallis non-parametric ANOVA test was performed to test whether there is a difference among pre-surgical ionized calcium. It was found that there is not enough evidence to reject the null hypothesis, thus there is no difference in the pre-surgical ionized calcium results among patients (*p-value* = 0.982; Adjusted for ties *p-value* = 0.852).

Table 4.9 Mean and standard deviation for pre-surgical ionized calcium (mmol/L)

	Population	*Type 1*	*Type 2*	*Type 3*	*Type 4*
Mean	*1.169*	*1.171*	*1.168*	*1.098*	*1.196*
Standard Deviation	*0.107*	*0.106*	*0.109*	*0.097*	*0.040*

As it was found for plasma calcium, the pre-surgical ionized calcium results do not correlate with the presence of postsurgical complications.

4.5.2 Analysis of Ionized Calcium's Drop Phase

During the drop phase, patients experienced a drop in the ionized calcium. On average, the ionized calcium drops until it reaches 0.936 mmol/L (σ = 0.089) and then starts to return back to normal. This minimum is reached, for almost 95% of the patients, within the first 24 hours after surgery (μ = 0.5463 days; σ = 0.2637 days). Commonly, during cardiovascular surgery, patients receive free calcium intravenously, but not post-operatively.

When intravenous calcium gluconate is administered, the rise in ionized calcium is small and of very short duration, with the ionized calcium quickly returning to the previously depressed levels.

Table 4.10 summarizes the values of $T\text{-}IC_{DP\text{-}min}$ and $ICa_{DP\text{-}min}$ for the patients included in the study. These data suggest that the ionized calcium regulatory system may be "reset" resulting in a decrease in both ionized and total calcium.

Table 4.10 Mean and standard deviation for ionized calcium $T\text{-}ICa_{DP\text{-}min}$ and $ICa_{DP\text{-}min}$.

		Population	*Type 1*	*Type 2*	*Type 3*	*Type 4*
$ICa_{DP\text{-}min}$	*Mean*	*0.941*	*0.951*	*0.937*	*0.872*	*0.866*
	Standard Deviation	*0.089*	*0.086*	*0.089*	*0.068*	*0.136*
$T_{DP\text{-}min}$	*Mean*	*0.574*	*0.555*	*0.588*	*0.602*	*0.695*
	Standard Deviation	*0.237*	*0.211*	*0.255*	*0.149*	*0.429*

On average, the value of $ICa_{DP\text{-}min}$ is considerably lower for patients who died after surgery. A Kruskal-Wallis non-parametric ANOVA test was conducted to test if there is a significant difference in the values of $ICa_{DP\text{-}min}$ among patient types. The resulting *p-value* was 0.779 (adjusted for ties *p-value* = 0.295), therefore, the null hypothesis is accepted and it can be claimed that there is no statistical difference in the values of $ICa_{DP\text{-}min}$ among patient types.

The same procedure was carried out for ionized calcium's $T\text{-}ICa_{DP\text{-}min}$. As a result, it was found that there is not a significant difference in the values of $T\text{-}ICa_{DP\text{-}min}$ (*p-value* = 0.990, adjusted for ties *p-value* = 0.395) among patient types. Although, there is not sufficient statistically evidence to claim that there is a difference in the values of $T\text{-}Ca_{DP\text{-}min}$ and $ICa_{DP\text{-}min}$ for the patients included in the study, a slight difference is noticed in the mean values of $T\text{-}ICa_{DP\text{-}min}$ and $ICa_{DP\text{-}min}$. For $T\text{-}ICa_{DP\text{-}min}$ the values are higher for patients experiencing complications, whereas for $ICa_{DP\text{-}min}$ occurs the opposite.

The ionized slope during the drop phase could be an indicator of the effect of the surgery on the patients. Table 4.11 summarizes the ionized calcium slope during the drop phase for all patient types.

Table 4.11 Ionized calcium slope during the drop phase for all patient types

	Population	*Type 1*	*Type 2*	*Type 3*	*Type 4*
Mean	*-0.999*	*-1.005*	*-0.976*	*-1.187*	*-1.359*
Standard Deviation	*1.425*	*1.150*	*1.668*	*1.168*	*0.774*

After performing a Kruskal-Wallis non-parametric ANOVA test on the data, it was found that there is not a significant difference in the values of the slopes of ionized calcium during the drop phase (*p-value* = 0.999; adjusted for ties *p-value* = 0.489) among patient types. However, it can be noticed that the steepness on the drop of ionized calcium for patients who died during the perioperative period is higher.

Although, there is not enough statistical evidence, there are some hints that can help in assessing patient condition. High negative slopes can be the consequence of the direct effect of the operation. Notice that the same conclusions were drawn for plasma calcium during the drop phase.

4.5.3 Cross Correlation Analysis between Plasma and Ionized Calcium

It is observed that postsurgical plasma and ionized calcium show a similar behavior over time. Both present a noticeable drop during the perioperative period and then start to return back to normal. A cross correlation analysis is performed to test the relationship between the time series of plasma and ionized calcium results. The time series created for this purpose are based on 12 hour-intervals. Figure 4.7, shows the frequency distribution of correlation between postsurgical plasma and ionized calcium.

On average, the correlation between both time series is 0.41 across the patient population without performing any shifting on the time series (lag = 0). This average is highly influenced by the heavy tail to the left on the frequency distribution. In general, a

large portion of the population (70%) shows a correlation greater than 40% between both time series, indicating that both time series behave approximately the same during the postsurgical period.

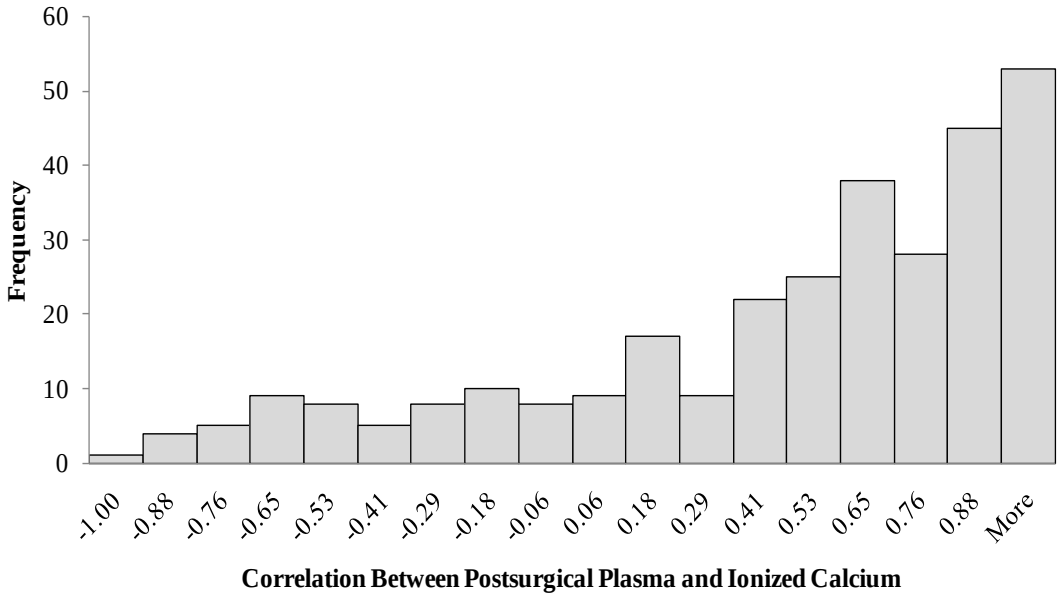

Figure 4.7 Frequency of correlations between postsurgical plasma and ionized calcium

For 19% of the patients on the study there is a negative correlation between plasma and ionized calcium. This may be due to the administration of medications containing calcium. It is expected that if this effect is blocked the correlation will increase positively. Unfortunately, there are a series of factors, such as the effect of treatments, diet, metabolism and comorbidities, that affect the behavior of postsurgical laboratory test results. This reality makes difficult the identification of possible sources of variability in laboratory tests since we do not have access to other possible contributing factors

4.6 Platelet Count: Reference Ranges

According to the USMLE [19] the reference range for platelet count is from 150,000 to 450,000 per milliliter. Just as it was calculated for plasma calcium, reference ranges

for the population of this study are developed based on test results. Initially, the last result before undergoing surgery was extracted from the dataset for each patient. Figure 4.8 shows the frequency distribution of the pre-surgical platelet count.

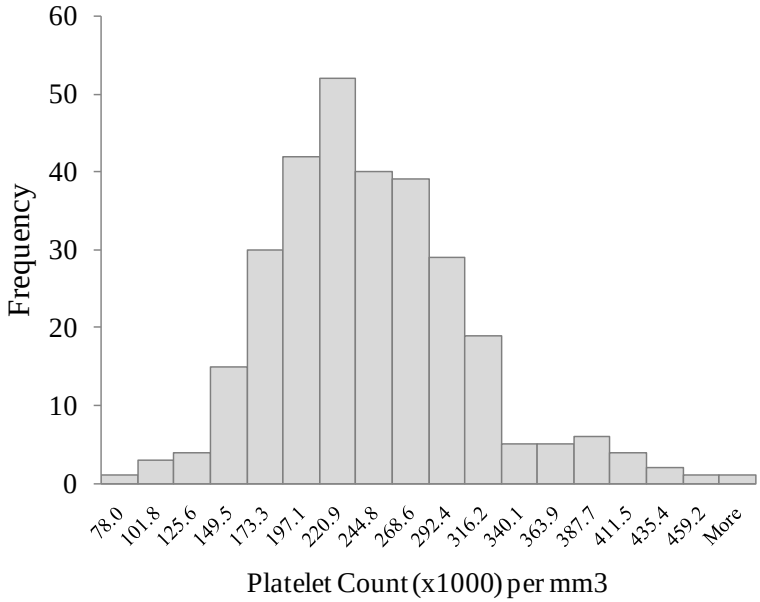

Figure 4.8 Frequency distribution of pre-surgical platelet count of the studied population

The reference range for the population of this study is [99,270 – 359,362] platelets per milliliter (μ = 229,320; σ=65,021). The frequency distributions found in the literature differ appreciably from the results obtained by constructing this reference range for platelet count (mean ± 2σ). Although, the platelet count frequency distribution shows a fairly Gaussian shape, the hypothesis of normality was rejected after performing a Kolmogorov-Smirnov test (where the test statistic was equal to 0.0658 and the corresponding p-value was equal to 0.0607), due to presence of some outliers that create a heavy tailed frequency distribution.

Even though the normality assumption was rejected, it is possible that, if the number of samples increases, the data could be modeled as a normal. Still it is important to

determine whether baseline differences among the different type of patients are significant. Results from the four groups were compared using a Kruskal-Wallis test and further analyzed by applying individual Wilcoxon tests between pairs of groups as a "post-hoc" test, just as it was done for plasma calcium. A summary of the results is presented in table 4.12 and 4.13.

Table 4.12 Mean and standard deviation for pre-surgical platelet count (mg/dl)

	Population	*Type 1*	*Type 2*	*Type 3*	*Type 4*
Mean	*229.32*	*234.15*	*226.89*	*203.60*	*191.20*
Standard Deviation	*65.02*	*62.92*	*66.66*	*76.66*	*60.21*

Table 4.13 p-values from a two-sample Wilcoxon rank sum test for pre-surgical platelet count

Patient Type	*P-Values*
Type 1 - Type 2	*0.325*
Type 1 - Type 3	*0.458*
Type 1 - Type 4	*0.152*
Type 2 - Type 3	*0.629*
Type 2 - Type 4	*0.245*
Type 3 - Type 4	*0.676*

The results from the two-sample Wilcoxon rank sum test showed that there are not significant differences between the pre-surgical platelet count among patient types. However, it is noticeable that the lowers *p-values* correspond to the comparison between patient groups 1 and 4, and 2 and 4, which are the most dissimilar types of patients, since patients type 1 and 2 survived and patient type 4 died during the perioperative period. Also, the higher *p-values* are associated to the comparison between patient type 2 and 3, and 3 and 4. In the first case, the relation may be caused by the fact that these 2 patient populations had complications during the postsurgical period and in the second case because they both died.

As a conclusion, the pre-surgical platelet count does not provide enough statistical confidence to associate it to the likelihood of postsurgical complications. However, an expected difference is observed on the mean of the patient groups where the pre-surgical platelet count is lower for patients who had complications or died.

4.7 Platelet Count: Initial and Global Minimums

A decrease in platelet is anticipated for patients who underwent cardiovascular surgery due to their consumption during the wound healing. In this study, platelet count levels drop below the lower bound of the reference range for the majority of the patients. As it was defined for plasma calcium, $P_{DP\text{-}min}$ represents the platelet count level when the initial minimum is reached. For plasma calcium this value is reached, in average, during the second day after surgery, day where the $Ca_{DP\text{-}min}$ occurs. This event shows that both test results fall dramatically during the first day after surgery, reaching their minimum at the second day, which becomes a critical day for the patient care. For patients with a satisfactory recovery process, once the minimum is reached, the platelet count goes back to values within the reference range. Results from patients who experienced complications do not show this behavior; for them, the platelet count drops again, to levels even lower level than the initial. As it was assumed for plasma calcium, $P_{G\text{-}min}$ is expected to be the same as $P_{DP\text{-}min}$, for patient's type 1 and 4. Table 4.14 presents a summary of the average values for $P_{DP\text{-}min}$ and $P_{G\text{-}min}$.

Table 4.14 Mean and standard deviation for $P_{DP\text{-}min}$ and $P_{G\text{-}min}$ for all patient types (mg/dl)

		Population	*Type 1*	*Type 2*	*Type 3*	*Type 4*
$P_{DP\text{-}min}$	*Mean*	*132.09*	*134.07*	*130.17*	*69.60*	*135.20*
	Standard Deviation	*56.28*	*55.57*	*50.94*	*20.21*	*56.89*
$P_{G\text{-}min}$	*Mean*	*122.09*	*125.50*	*119.27*	*55.40*	*124.20*
	Standard Deviation	*50.24*	*47.55*	*47.12*	*24.93*	*61.28*

The mean value of $P_{G\text{-}min}$ for patients' type 3 is the lowest. These values are mostly captured prior to the patient's death. These results differ significantly from the other patients' types. It is noticeable that for patient type 1, 2 and 4, $P_{G\text{-}min}$ is about the same even when their recovery process and outcome differ. Since patients type 4 died during the perioperative period, it is possible that their platelet count levels did not have time to show a large decrease, since the main consumption of platelets occurs during the recovery phase (when the complications during the wound healing process appear most frequently). . Figures 4.9 and 4.10 show the frequency distribution of $P_{G\text{-}min}$ and $P_{DP\text{-}min}$ respectively.

Both frequency distributions show a skewed Gaussian shape, which results in the normality assumption not holding in this case. To test whether there is a significant difference between $P_{G\text{-}min}$ and $P_{DP\text{-}min}$ for all patient types, a two-sample Wilcoxon rank sum test was performed. Results are shown in table 4.15.

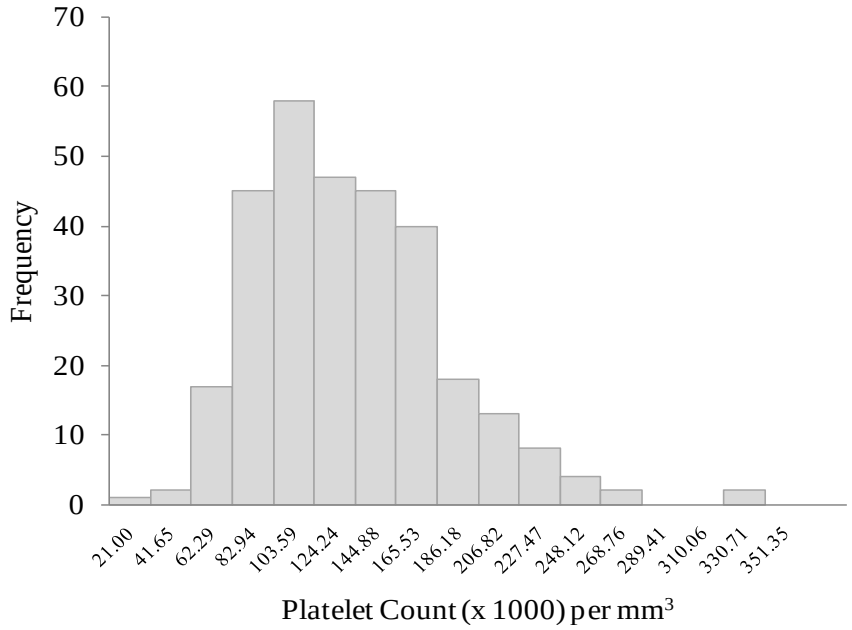

Figure 4.9 Frequency distribution of $P_{G\text{-}min}$

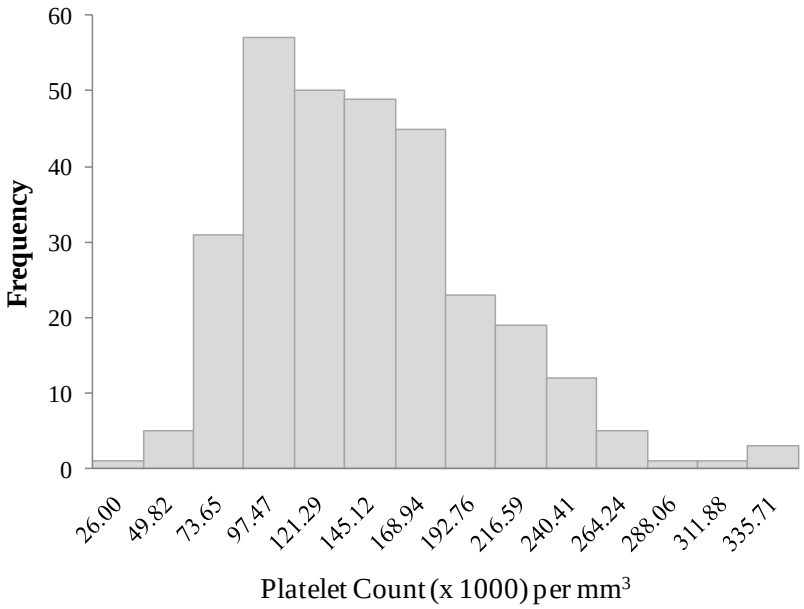

Figure 4.10 Frequency distribution of $P_{DP\text{-}min}$

The test results showed no significant difference in the values of minimum values of $P_{G\text{-}min}$ and $P_{DP\text{-}min}$, for patient type 1, 2 and 4. This implies that for these patient types, the $P_{DP\text{-}min}$ corresponds to their $P_{G\text{-}min}$ in the majority of the cases. Based on these results, the platelet count level for patients' type 2 is not expected to drop below their $P_{DP\text{-}min}$ after the drop phase, if it drops below $P_{DP\text{-}min}$ it is a clear symptom of the severity of the complication. $P_{G\text{-}min}$ and $P_{DP\text{-}min}$ results from patients' type 3 are significantly different from the results from other patient types.

Table 4.15 p-values from a two-sample Wilcoxon rank sum test of $P_{G\text{-}min}$ and $P_{DP\text{-}min}$

	p-values	
Patient Type	$P_{G\text{-}min}$	$P_{DP\text{-}min}$
Type 1 - Type 2	*0.3191*	*0.7589*
Type 1 - Type 3	*0.0009*	*0.0028*
Type 1 - Type 4	*0.91*	*0.8422*
Type 2 - Type 3	*0.0018*	*0.004*
Type 2 - Type 4	*0.9748*	*0.8536*
Type 3 - Type 4	*0.0758*	*0.0758*

A single value of platelet count does not provide enough information to establish whether a patient is suffering complications or not, since there is not a significant difference between the results of patient type 1 and 2. However, for patients' type 3 it can be noticeable lower values of $P_{G\text{-}min}$ and $P_{DP\text{-}min}$ that for others, a single markedly decreased level after the drop phase it can be interpreted as a sign of possible complications on the patient recovery. Also, this suggests that a temporal analysis of platelet count should be performed to confirm the appearance of complications.

4.8 Platelet Count: $T\text{-}P_{G\text{-}min}$ and $T\text{-}P_{DP\text{-}min}$

The time to reach the $P_{DP\text{-}min}$ ($T\text{-}P_{DP\text{-}min}$), is an important indicator to consider since small values represent a rapid drop of platelet count caused by internal bleeding. Also, large values could indicate that patient platelet production is enough to successfully heal the wounds after surgery, indicating a mild effect of the surgery on its levels. As it was stated for plasma calcium, the $T\text{-}P_{G\text{-}min}$ should differ among patient's groups due to the late appearance of complications for patients' type 2 and 3 during the recovery phase. It is expected that $T\text{-}P_{G\text{-}min}$ for these patients will be considerably larger than their $T\text{-}P_{DP\text{-}min}$. Figure 4.11, 4.12 and table 4.16 show the behavior of $T\text{-}P_{DP\text{-}min}$ and $T\text{-}P_{G\text{-}min}$ for the population of this study.

Table 4.16 Mean and standard deviation for $T\text{-}P_{DP\text{-}min}$ and $T\text{-}P_{G\text{-}min}$

		Population	*Type 1*	*Type 2*	*Type 3*	*Type 4*
$T\text{-}P_{DP\text{-}min}$	*Mean*	*2.162*	*2.113*	*2.198*	*3.177*	*0.942*
	Standard Deviation	*1.295*	*1.154*	*1.367*	*1.563*	*0.803*
$T\text{-}P_{G\text{-}min}$	*Mean*	*4.205*	*3.823*	*4.406*	*4.119*	*1.029*
	Standard Deviation	*5.790*	*4.958*	*6.346*	*1.673*	*0.350*

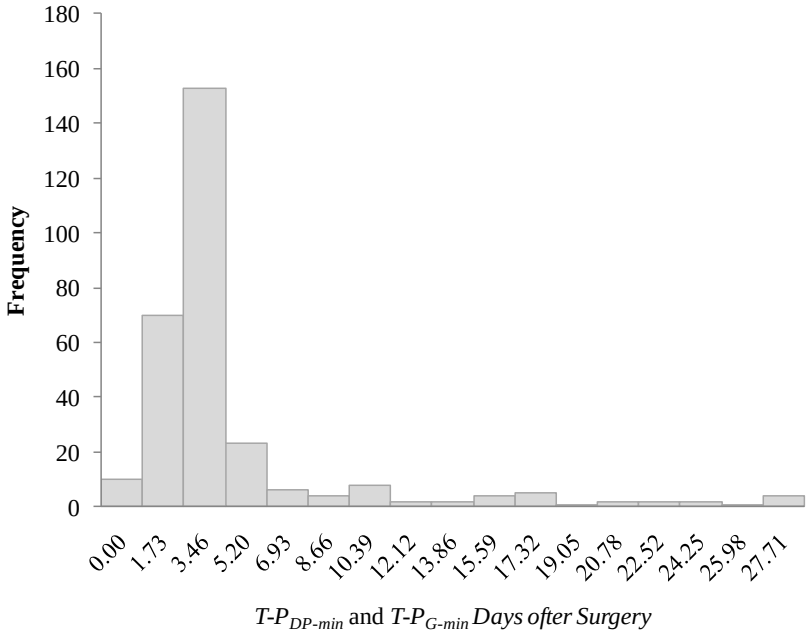

Figure 4.11 Frequency distribution of $T\text{-}P_{G\text{-}min}$

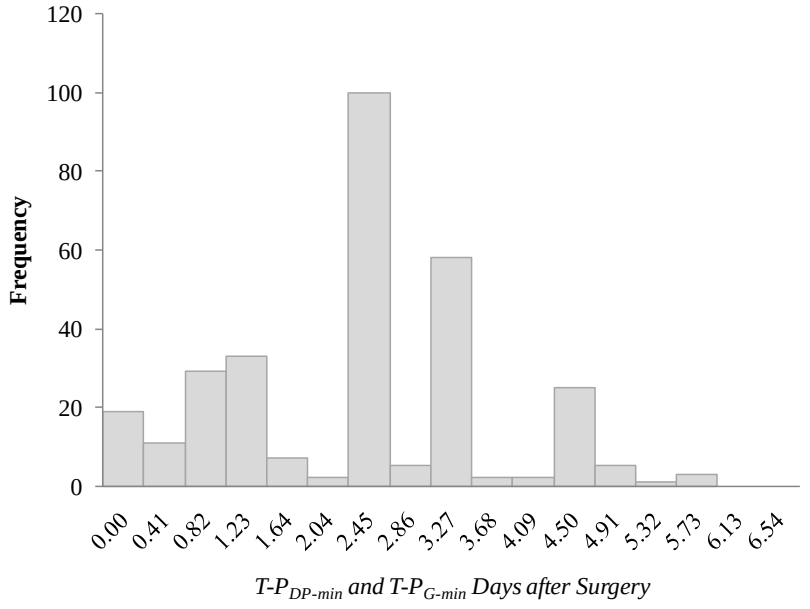

Figure 4.12 Frequency distribution of $T\text{-}P_{DP\text{-}min}$

The mean value for $T\text{-}P_{DP\text{-}min}$ shows that the end of the drop phase occurs, on average, at the beginning of the second day, just as it was found for plasma calcium. However, the means among patient groups differ, in the case of patient type 1 and 2 just by a few hours,

indicating that there is not a marked difference in the values of $T\text{-}P_{DP\text{-}min}$ for these patient groups. On the other hand, for patients on group 3 the minimum occurred on average at the beginning of the third day.

The values of $T\text{-}P_{G\text{-}min}$ show a considerable difference among patient groups. For patients who experienced complications, the value of $T\text{-}P_{G\text{-}min}$ occurred at the fourth day after surgery, while for patients' type 1 at the third. A two-sample Wilcoxon rank sum test was performed to test the differences among the values of $T\text{-}P_{DP\text{-}min}$ for all patient types. The same analysis was carried out for $T\text{-}P_{G\text{-}min}$. Results are summarized in table 4.17.

Table 4.17 p-values from a two-sample Wilcoxon rank sum test of $T\text{-}P_{G\text{-}min}$ and $T\text{-}P_{DP\text{-}min}$

	p-values	
Patient Type	$T\text{-}P_{G\text{-}min}$	$T\text{-}P_{DP\text{-}min}$
Type 1 - Type 2	*0.5883*	*0.6388*
Type 1 - Type 3	*0.4013*	*0.1361*
Type 1 - Type 4	*0.6945*	*0.0282*
Type 2 - Type 3	*0.4323*	*0.1458*
Type 2 - Type 4	*0.8371*	*0.0419*
Type 3 - Type 4	*0.754*	*0.0367*

In general there is not a significant difference in the value of $T\text{-}P_{G\text{-}min}$ among patient groups, indicating that all the patients experience a similar drop in platelet count after cardiovascular surgery. This event also indicates that platelet count results are more variable than plasma calcium overtime after the drop phase. However, there is a significant difference in the values of $T\text{-}P_{DP\text{-}min}$ among patients who died during the perioperative period and the rest of them. This is an indicator that the platelet count drops dramatically for these patients. This drop may be caused for complications during the surgery associated with internal bleeding.

The analysis of the variation of platelet count over time gives important information to assess patient condition. Physicians can monitor the plasma calcium based on its variation, having as reference the lowest level and the instance when it occurred. Just as it was found for plasma calcium, a negative trend should trigger an alarm, indicating that there is a risk of dropping to levels close to the $P_{DP\text{-}min}$. As it was shown in table 4.15, the decreasing trend in platelet count results should end by the third day if the recovery process is satisfactory. The next section presents a deeper analysis of the variation of platelet count over time, but focusing on tits slope during the drop and recovery phase.

4.9 Platelet Count Slopes during the Drop and Recovery Phases

The analysis of the variation of platelet count could help in the timely identification of postsurgical complications associated with bleeding and coagulation problems. The analysis will be based on the construction of a data set with the platelet count slopes during the drop and recovery phase. Table 4.18 shows the mean and standard deviation of the platelet count during the drop and recovery phase for the population of this study.

Table 4.18 Platelet count slopes during the drop and recovery phase for all patient types

		Slope Drop Phase	*Slope T-$P_{DP\text{-}min}$ - 7th Day*
Population	*Mean*	*-16.728*	*0.037*
	Std. Dev.	*29.620*	*0.078*
Type 1	*Mean*	*-17.417*	*0.043*
	Std. Dev.	*27.194*	*0.072*
Type 2	*Mean*	*-13.559*	*0.036*
	Std. Dev.	*20.394*	*0.085*
Type 3	*Mean*	*-17.027*	*0.015*
	Std. Dev.	*7.246*	*0.032*
Type 4	*Mean*	*-71.689*	-
	Std. Dev.	*113.193*	-

As shown in table 4.18, platelet count results have a negative slope for all patient types during the drop phase. This behavior shows that there is a decrease in platelet count for all patient types, but for patients' type 4 it is steeper. As it was assumed before, this behavior may be due to the presence of a massive loss of blood.

A two-sample Wilcoxon rank sum test was performed to test the difference of the platelet count slope during the drop and recovery phase for all patient types. The results from this analysis are shown in table 4.19.

Table 4.19 p-values from a two-sample Wilcoxon rank sum test of the plasma calcium slope during the drop and recovery phase for all patient types

	p-values	
Patient Type	*Slope Drop Phase*	*Slope $T_{DP\text{-}min}$ - 7th Day*
Type 1 - Type 2	*0.9611*	*0.6543*
Type 1 - Type 3	*0.4714*	*0.2159*
Type 1 - Type 4	*0.9391*	-
Type 2 - Type 3	*0.5685*	*0.3366*
Type 2 - Type 4	*0.8887*	-
Type 3 - Type 4	*0.8345*	

The behavior of the platelet count (slope) during the drop phase is the same for all patients, as it was confirmed for plasma calcium. However, although there is not a significant difference in the values of slope during the recovery phase, it can be noticeable that the p-values are lower when results from the comparison between patients type 1 and 3, and 2 and 3; indicating that the slope for patients type 3 is steeper. Notice that the comparisons were made between type 1, 2 and 3, since type 4 patients died before this phase.

The recovery pattern of platelet count, following the initial minimum, appears to be a useful indicator for assessing patient recovery. Since there is not a marked difference

among patients during the drop phase, differences in patient condition start to be recognized after the platelet count reaches the $P_{DP\text{-}min}$. If the test results do not show the expected ascending trend during the recovery phase, it can be assumed as an indicator of an unrecognized complication on patient condition. This is even more critical if the test results are close to the lower bound of the reference range or to the $P_{DP\text{-}min}$. For almost all the patients the value of $P_{DP\text{-}min}$ was below the lower bound of the reference range, validating the usefulness of this benchmark.

Chapter 5: Time Series Clustering of Laboratory Test Results

This chapter describes the performance of the proposed methodology for the analysis of laboratory test results, as well as the description of the procedure for the construction of the time series of laboratory test results and then, the patient clustering analyses as well as considerations for practical use of the methodology are shown.

5.1 Construction of Datasets of Laboratory Test Results

Based on the results from the previous chapter, it is noticeable the direct relationship between the results of plasma calcium and ionized calcium. Due to the high correlation between plasma calcium and ionized calcium, ionized calcium is not included in the multivariate clustering analysis. Consequently the multivariate clustering analysis is based on plasma calcium and platelet count test results over time

For both tests, 8 different time series were constructed, based on data transformations and data manipulation to avoid missing data. Since the data was not uniformly sampled, it was not possible to perform a time series analysis with the data as is; it was necessary to perform mathematical transformations on the data to have equally time-spaced observation. To achieve this goal, three interpolation methods were applied on the data, namely linear interpolation, polynomial interpolation and splines. Linear interpolation provided the best fit in modeling the trends on the data set for both tests. When polynomial and splines were used, the estimation have more than n -1 degrees of freedom, which resulted in curves that were not similar to the tendencies observed on the

laboratory test results overtime. The use of linear interpolation allowed a more accurate estimation of "missing values". Based on the results after the implementation of linear interpolation, the estimation of results was performed at equally-spaced points in time. A detailed description of the methodology for the construction of these 8 time series is presented below. For all datasets, the first value on this time series is the one associated to the last result before surgery (baseline).

- Linear Interpolation: The first data set was constructed using linear interpolation to estimate the test results every 12 hours. The first value on this time series is the one associated to the last result before surgery (baseline), and then the sequence of estimations every 12 hours, based on the previous and the subsequent result in the dataset at this points in time.
- Linear Interpolation (12 Hours): This dataset differs from the previous. To construct this dataset, a linear model was determined for to represent the behavior of the test results in 12 hours intervals. Then, the model was used to estimate the results every 12 hours.
- Linear Interpolation (24 Hours): This dataset differs from the previous one just in the fact that the linear model was determined for to represent the behavior of the test results in 24 hours intervals. Then, the model was used to estimate the results every 24 hours.
- Rate of Change: Based on the results from the first dataset (Linear Interpolation), a new dataset with the rate of change of results were constructed using equations 3.3 and 3.4.

- Rate of Change (12 Hours): Same as previous dataset but using as a reference the Linear Interpolation (12 Hours) dataset.
- Rate of Change (24 Hours): Same as previous dataset but using as a reference the Linear Interpolation (24 Hours) dataset.
- Time Intervals: Based on the experience of physicians in the committee, they stated that it is expected that at the third day after surgery the patient should leave the ICU. Then, at the sixth day it is expected that the patient is ready to perform routine tests to authorize the discharge by the seventh day. If the patient stays longer than 7 days, this may be an indicator of some complications or a slow recovery. Then it seemed appropriate to construct a dataset estimating results every 3 days. So, this time series starts with the baseline value, and then a linear model was determined for to represent the behavior of the test results in 3 hours intervals, from 0 to the 3^{rd} day after surgery, from the 3^{rd} day to the 6^{th}, and from the 9^{th} to the 12^{th}. Patients that stayed longer than 12 days are considered as patients who experienced complications.
- Segments: In the previous chapter, some features of laboratory test results were identified. One of them is $T_{DP\text{-}min}$, which will be used as a reference to create this dataset. Once again, a linear model was created with the data points within the day of surgery and the $T_{DP\text{-}min}$. Then, a model between $T_{DP\text{-}min}$ and time where the results go back within the reference range. Then the procedure is the same as it was shown for the Time Intervals dataset.

Several time series clustering techniques were applied to all the constructed datasets such as fuzzy logic based C-Means, Hierarchical and K-Means. Since for this setting it is difficult to draw hard partition conclusions, regarding the potential risk of complications,

fuzzy logic techniques are used to model the recovery process of patients after cardiovascular surgery. The next section describes the results after the implementation of the proposed methodology.

5.2 Multivariate Time Series Clustering

The implementation of multivariate time series clustering techniques provides a representation of the potential risks that patients suffer during their stay in the SICUs. By calculating these membership values, and then segmenting them by patient group, patient risk profiles can be generated. If the constructed clusters allow the identification of recovery patterns for the patient types defined before, then timely interventions can be performed for patients that are expected to have complications.

Results from the implementation of multivariate clustering techniques are summarized in tables 5.1, 5.2 and 5.3. Table 5.1 shows the membership values obtained after the implementation of fuzzy logic clustering, table 5.2 fuzzy C-Means and 5.3 fuzzy K-Means.

Fuzzy clustering does not yield "perfectly" classify patients according to their outcomes, maybe due to the similarities of the time series during the drop phase among patient types. On the other hand linear interpolation classified all patients that suffered complications in the same cluster. However, it classifies on the same cluster around half of patients' type 1 and 2, showing that this data set is not able to fully capture signs of possible complications that might his death. The same situation is observed if the time intervals and the segments based datasets are used. Also, around half of the patients who survived after surgery are classified on the cluster 1, where almost all the patients who died were classified.

The dataset that appear to better capture the patients' likelihood of having complications is the rate of change.

Table 5.1 Time series fuzzy clustering results

Classification	Fuzzy Logic (Linear Interpolation)	Fuzzy Logic (Linear Interpolation 12 Hours)	Fuzzy Logic (Linear Interpolation 24 Hours)	Fuzzy Logic (Rate of Change)
Type 1 in Cluster 1	0.55	0.45	0.54	0.27
Type 2 in Cluster 1	0.59	0.56	0.56	0.29
Type 3 in Cluster 1	1.00	1.00	1.00	0.60
Type 4 in Cluster 1	1.00	0.75	1.00	1.00
Type 1 in Cluster 2	0.45	0.55	0.46	0.73
Type 2 in Cluster 2	0.41	0.44	0.44	0.71
Type 3 in Cluster 2	0.00	0.00	0.00	0.40
Type 4 in Cluster 2	0.00	0.25	0.00	0.00

Classification	Fuzzy Logic (Rate of Change 12 Hours)	Fuzzy Logic (Rate of Change 12 Hours)	Fuzzy Logic (Segments)	Fuzzy Logic (Time Intervals)
Type 1 in Cluster 1	0.27	0.27	0.48	0.55
Type 2 in Cluster 1	0.29	0.29	0.51	0.65
Type 3 in Cluster 1	0.60	0.60	1.00	1.00
Type 4 in Cluster 1	1.00	1.00	0.75	1.00
Type 1 in Cluster 2	0.73	0.73	0.52	0.45
Type 2 in Cluster 2	0.71	0.71	0.49	0.35
Type 3 in Cluster 2	0.40	0.40	0.00	0.00
Type 4 in Cluster 2	0.00	0.00	0.25	0.00

Table 5.2 Time series fuzzy C-Means clustering results

Classification	Fuzzy Logic C-Means (Linear Interpolation)	Fuzzy Logic C-Means (Linear Interpoaltion 12 Hours)	Fuzzy Logic C-Means (Linear Interpoaltion 24 Hours)	Fuzzy Logic C-Means (Rate of Change)
Type 1 in Cluster 1	0.36	0.70	0.61	1.00
Type 2 in Cluster 1	0.34	0.71	0.69	0.99
Type 3 in Cluster 1	0.00	1.00	1.00	1.00
Type 4 in Cluster 1	0.25	0.75	0.75	1.00
Type 1 in Cluster 2	0.64	0.30	0.39	0.00
Type 2 in Cluster 2	0.66	0.29	0.31	0.01
Type 3 in Cluster 2	1.00	0.00	0.00	0.00
Type 4 in Cluster 2	0.75	0.25	0.25	0.00

Classification	Fuzzy Logic C-Means (Rate of Change 12 Hours)	Fuzzy Logic C-Means (Rate of Change 12 Hours)	Fuzzy Logic C-Means (Segments)	Fuzzy Logic C-Means (Time Intervals)
Type 1 in Cluster 1	1.00	1.00	0.66	0.56
Type 2 in Cluster 1	0.99	0.99	0.68	0.69
Type 3 in Cluster 1	1.00	1.00	1.00	1.00
Type 4 in Cluster 1	1.00	1.00	0.75	0.75
Type 1 in Cluster 2	0.00	0.00	0.34	0.44
Type 2 in Cluster 2	0.01	0.01	0.32	0.61
Type 3 in Cluster 2	0.00	0.00	0.00	0.00
Type 4 in Cluster 2	0.00	0.00	0.25	1.00

Table 5.3 Time series fuzzy K-Means clustering results

Classification	Fuzzy Logic K-Means (Linear Interpolation)	Fuzzy Logic K-Means (Linear Interpolation 12 Hours)	Fuzzy Logic K-Means (Linear Interpolation 24 Hours)	Fuzzy Logic K-Means (Rate of Change)
Type 1 in Cluster 1	0.27	0.22	0.28	0.00
Type 2 in Cluster 1	0.21	0.14	0.23	0.01
Type 3 in Cluster 1	0.00	0.00	0.00	0.00
Type 4 in Cluster 1	0.00	0.25	0.25	0.00
Type 1 in Cluster 2	0.73	0.78	0.72	1.00
Type 2 in Cluster 2	0.79	0.86	0.77	0.99
Type 3 in Cluster 2	1.00	1.00	1.00	1.00
Type 4 in Cluster 2	1.00	0.75	0.75	1.00

Classification	Fuzzy Logic K-Means (Rate of Change 12 Hours)	Fuzzy Logic K-Means (Rate of Change 12 Hours)	Fuzzy Logic K-Means (Segments)	Fuzzy Logic K-Means (Time Intervals)
Type 1 in Cluster 1	0.00	0.00	0.77	0.38
Type 2 in Cluster 1	0.00	0.00	0.80	0.23
Type 3 in Cluster 1	0.00	0.00	1.00	0.00
Type 4 in Cluster 1	0.00	0.00	0.75	0.25
Type 1 in Cluster 2	0.00	0.00	0.23	0.62
Type 2 in Cluster 2	0.00	0.00	0.20	0.77
Type 3 in Cluster 2	0.00	0.00	0.00	1.00
Type 4 in Cluster 2	0.00	0.00	0.25	0.75

When it is used around of 70% of the patients who survive are classified on the same group and just a 40% of the patients who died after complications where also classified on that group. The results above show that when using fuzzy K-Means and fuzzy C-means the majority of the patients were mostly classified in the same cluster. This classification maybe due to the fact that all patients' groups presented a similar behavior during the drop phase and during the recovery phase, thus the methods are unable to determine differences on the time series. Most of the patients type 4 were classified together due to their similarities in the steepness of their slope during the drop phase. This classification was expected since the slopes during this phase appear to be steeper than for the other patients in other groups.

The best performance of the methods is achieved when the rate of change every 12 hours is used to generate the clusters, since better membership values are obtained. All the patients who survived the perioperative period are included in the cluster. Also when

the clusters are created less overlapping is observed when fuzzy clustering techniques are used.

Overall the three fuzzy methods utilized did not fully capture differences between patient types 1 and 2. Patients type 1 and 2 presented very similar trends on their laboratory tests results even after the drop phase. For most of these patients it is very difficult to identify whether they have complications or not just by interpreting their platelet count or plasma calcium. This is due to the different type of complications that are reported during patients' stay in the clinic. Many of the detected complications are not directly related to the levels of plasma calcium or platelet count; it is possible that the attending physicians identified them based on a different test, or based experience. Some of the complications found on the patient population were reported as follows in the information system: digestive system complication, pneumonia, arterial fibrillation, systemic sepsis, urinary tract infection, pleural effusion, anemia, chest pain, stroke, pulmonary insufficiency, acute renal failure, tachycardia, hypertension, reoperation for bleeding, myocardial infarction, intubation, cardiac arrest, metabolic encephalopathy, aortic valve disorder, acute lung edema, tracheotomy, asphyxia, and urine retention (more than 50 different types of complications were listed on the database).

Because the nature of these complications lies with the reaction of the different patients to the surgery, it is difficult to timely identify all of them with the information provided by just two tests. However, since low platelet count, or a quick drop on it, are related to complications such as internal bleeding, physicians could anticipate platelet count related complications if its levels are regularly checked to confirm whether the results are within the reference range and if the slope do not appear to be too steep. The

same conclusion can be draw for plasma calcium due to? its relationship with the mechanical function of the heart. Therefore complications related with mechanical failure such as strokes and chest pains can be anticipated by monitoring plasma calcium levels.

Regarding the number of clusters, several tests have been performed to evaluate what should be the appropriate number of clusters that should be included on the study. It would be expected that, since the patients were classified in 4 categories, type 1, 2, 3 and 4, the best scenario is the one where all patients from the same type were classified in a different cluster with membership values close to 1. If 4 clusters are constructed, all the membership values tend to be equal to 0.25, which means that there is equal probability to the patient to belong to each cluster. A similar situation occurred when 3 clusters are designed, but in this case the membership values were close to 0.33. Figures 5.1 and 5.2 show the performance of the clustering techniques for one of the resulting datasets. It is notice that when 2 clusters are used the overlapping is less.

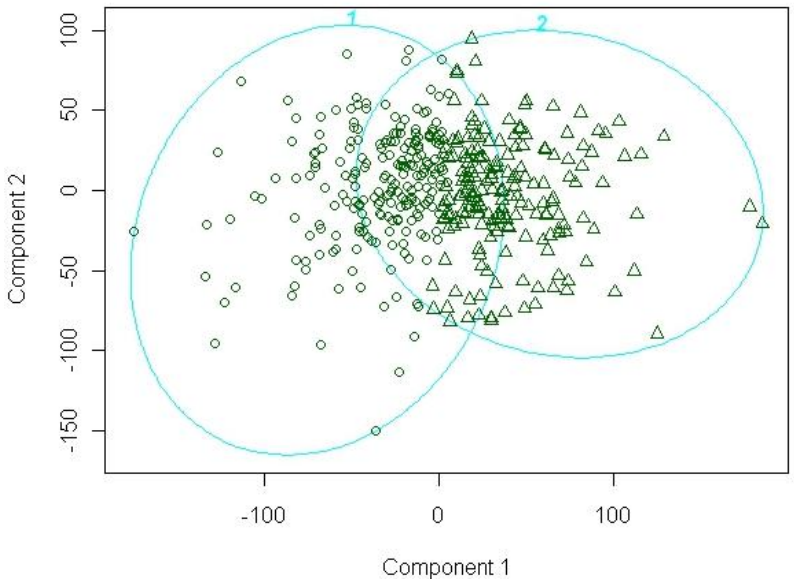

Figure 5.1 Fuzzy Logic Clustering (linear interpolation 12 hours), K=2

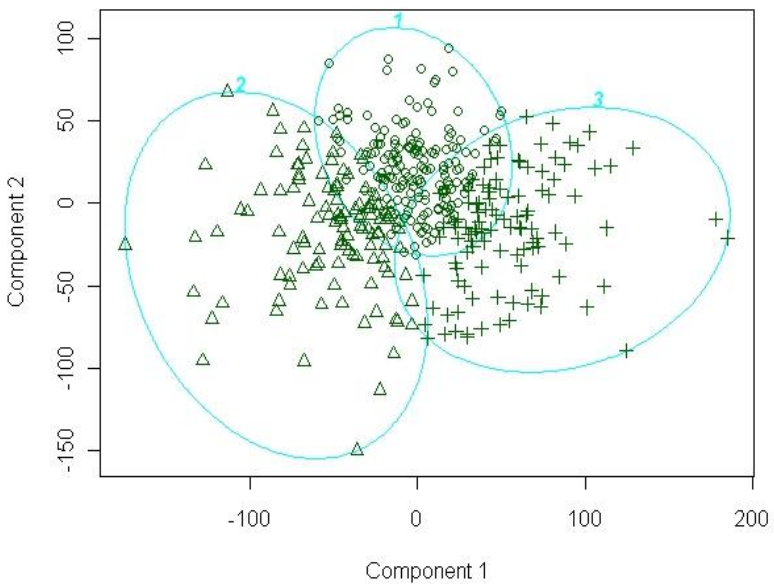

Figure 5.2 Fuzzy Logic Clustering (linear interpolation 12 hours), K=3

When K is increased, more fuzziness is introduced without increase the interpretation power. Based on the experimentation, best results were obtained when the rate of change is used instead of just the actual laboratory test result data. It is important to highlight that even though one of the objectives in implementing fuzzy logic is to obtain some fuzziness, if K increases over 2 the results will not provide us with useful information about the behavior of the patients. The same results are obtained when other methods are used.

Since the fuzziness is too high when more than 2 clusters are used, the best scenario is when patients who did not die where classify in the same group and the remaining in the other. However, since there are similarities between patients who died after complications and the ones who did not die after complications this goal may be partially achievable.

Further research efforts should include more tests in the analysis to find their key features that help physicians in better detect suspicious patterns associated to complications during patients' recovery after cardiovascular surgery.

Chapter 6: Conclusions and Future Work

The analysis of postsurgical plasma calcium provides valuable information to assist physicians while conducting patient monitoring. Plasma calcium tests results should be compared against the reference range to identify any signal that suggests a complication on patient condition. However, every time a test result is analyzed it should to be associated to the instance when the sample was taken. In this way the physician determines to which period the test corresponds, decreasing (drop phase) or back to normal levels (in the case of plasma calcium, around the 7th day after surgery).

It is expected that patients experience a consistent drop in plasma calcium and platelet count during the perioperative period. The average length of this period on patients who did not experienced complications is around 1 day for plasma calcium and 2 days for platelet count, indicating that at the end of the second day after surgery both results should show an increasing trend. If the test results continue dropping, it may indicate complications on the patient's condition.

The identification of different phases on patient recovery after cardiovascular surgery (drop, recovery and stabilization phase) would help physicians to timely identify unsafe patterns in plasma calcium and platelet count, associated to each of these phases. These unsafe patters in both tests may be used as indicators of complications on the patient's condition. It was shown that all the patients behave fairly the same during the drop phase, since their plasma calcium levels, platelet count, $T\text{-}Ca_{DP\text{-}min}$ and $T\text{-}P_{DP\text{-}min}$ are

statistically the same. However, the values of $P_{DP\text{-}min}$ and $Ca_{DP\text{-}min}$ become a baseline to assess patient recovery. It is important to mention that all the patients that reached an initial minimum in their test results, and then had recurring drops during the recovery phase, where reported as patients experiencing complications in the NSQIP records. These complications were associated to different causes, so it is difficult to identify whether the complication was mild or severe, or its effect on the patient's outcome.

Several patients had more than one complication during their stay on the clinic. The same patient could present episodes of tachycardia, sepsis, anemia or some other complication at the same time or during his stay in the clinic. Yet what the records do not show is the severity of the complication, and as a consequence, the real cause of the complication that made the patient stay longer than the expected time in the clinic or die is not identifiable. Besides, the variety of the possible complications and their interactions make even more difficult to really understand the relationship of variations on test results and a specific complication.

It is also important to highlight that variations on laboratory test can be correlated over time. After performing a cross correlation analysis of the time series of test results of plasma calcium and ionized calcium, it was found a fairly high positive correlation (0.4), between both (plasma albumin and ionized calcium) even though there are several factors that affect the natural fall in both tests. For example the administration of free calcium intravenously during surgery, creates a peak on the ionized calcium results' time series.

The complications reported by physicians during the patient's stay in the clinic differ among patients. This creates a problem if physicians want to will be able to timely

identify them all, since not all of them can be easily detected by interpreting a single blood test. In addition, many of the detected complications are not directly related to the levels of a single test, instead they could be only be identified by the concurrent analysis of several pieces of information from blood test results, radiographies, among other screening procedures. However, the correct analysis of the appropriate indicator can be very useful in identifying complications on patients' condition. In the case of the population of study, the analysis of plasma calcium provides a good performance in detecting possible complications on patient's condition, if a transformation is performed on the data (calculation of the rate of change every 12 hours).

It is necessary to perform a deeper analysis on the data to increase the level of understanding of how to timely identify a complication on a patient. The data from the NSQIP allow us to know the set of complications that a patient suffered during his recovery, which could further help to segment the analyses by complication type to better profile the trends of each test included on the CBC and BMP. Also, data from the JAHVA includes information about patient's demographics that could provide with valuable information to construct a more comprehensive profile of the expected condition of a patient of a specific race, age and gender at the moment of the detection of a specific complication during the recovery process.

Since almost all patients included on this study that suffered complications had more than one, it is likely that many of these complications triggered others. It is important to understand the physiological process associated to the appearance of complication on a patient to be able to anticipate it effectively. For example, a low level of white cells could create the perfect situation for the appearance of infections of different kind that

could end with the patient death. Thus, key tests should be identified since they are markers of many of the most common complications, such as platelet count is clearly associated to bleeding, and then find the data transformation that better helps to extract valuable information from the data sets.

Future work will address the analysis of other laboratory tests that present a negative acute response to the surgery to identify if the behavior of the tests studied on this research is similar to the behavior of other test results. Also, the variations on plasma calcium, and other laboratory tests, may be associated to patients' characteristics such as race, age and gender. Further studies could be focused on the analysis of the relationship of these attributes and the recovery process of patients after undergoing cardiovascular surgery.

The methodology presented on this work can be replicated to analyze laboratory tests results associated to the monitoring process of patients after any surgical procedure. The main challenge for the user is to determine the appropriate set of tests that should be included on the analysis of patient postoperative condition.

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