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ANALYSIS AND EVALUATION OF A NOVEL RENAL TRANSPLANTATION PROGRAM. A CASE STUDY

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ABSTRACT

In 2011, a new and innovative collaborative program was established in Spain between the Autonomous Community of La Rioja and the Autonomous Community of the Basque Country in the matter of kidney transplant coordination, with the objective of increasing the number of kidney donors and the access of patients to kidneys for transplantation through a shared waiting list and a joint organization. Seven years after the foundation of the program, La Rioja had already transplanted 100 kidneys, and an analysis was carried out to assess its efficacy as well as some possible points for improvement.

To do so, data from all patients and donors involved in the 100 procedures were collected and examined, looking for possible indicators and reasons for the failure or success of each transplantation as a function of certain variables, such as the region were the kidneys were extracted or the distance and time that the organ had to travel before being implanted into the recipient.

It could be obtained from the achieved results that there were no significant differences in the outcomes of the patients based on the regions of origin of the kidneys, but a significant correlation was found between glomerular filtration rates (GFR) at the time of hospital discharge and the number of hours that the organs remained stored until being transplanted into the receptor.

After analyzing whether conditions of storage could affect somehow the overall function of the kidneys, it was concluded that the organ cooling mechanism during the process should be further controlled; the amount of time and conditions in which the organs remained stored affected their overall functionality at the date of hospital discharge, so La Rioja needs to concentrate on reducing such time in future procedures and improving the storage conditions of kidneys to provide better outcomes for their patients.

ACKNOWLEDGEMENTS

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1. INTRODUCTION

The Spanish National Transplant Organization (in Spanish, Organización Nacional de Trasplantes, ONT) was first created in 1989. Since 1992, Spain has become the world leader in organ donation and transplantation rates for 26 consecutive years, and donation rates as of 2017 have reached 47 pmp. This value corresponds to 19.2% all donations obtained in the European Union and 6.4% worldwide. Moreover, Spanish transplantation rates have also remained on top for the last two decades, reaching 113.4 transplants pmp in 2018 -a number significantly superior to the average of the European Union, at 66.9 pmp-. [1]

These outstanding results have been accomplished thanks to the introduction in 1989 of a new model, referred to as the "Spanish Model", and that has not only been carried out in our country, but also abroad in nations such as Portugal and Croatia, and with exceptional outcomes as well.

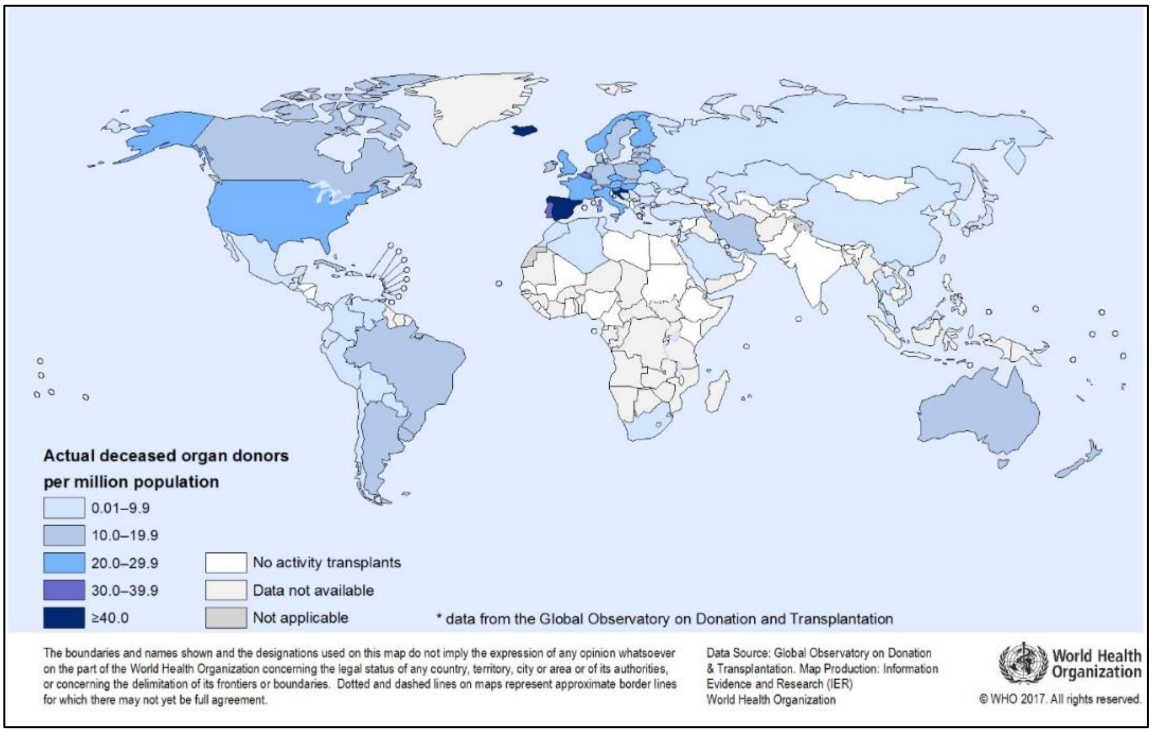


Fig. 1.1 World average distribution of deceased organ donors per million population *[40]*

Spain went from having 14 donors pmp in 1989 to the achieve current extraordinary rates and lead world rankings, and to understand this tremendous increase it is therefore essential to comprehend what the role of the Spanish National Transplant Organization has been, and the changes that have been caused by the implementation of the so-called ‘Spanish model’.

2. THE SPANISH MODEL AND THE NATIONAL TRANSPLANT ORGANIZATION

Immediately after its creation, the initial objective of the ONT was to establish an appropriate legal, economic, ethical, medical and political framework oriented to improving organ donation, and then put in place an efficient system to organize and coordinate all steps involved in the transplantation process.

To do this, the ONT introduced a network of transplant coordinators at three differentiated levels: national, regional and hospital. All of them were required to be medical doctors – generally intensive care doctors-, and worked in close contact with each other to ensure the optimal completion and tracking of all the transplantation process. Moreover, an enormous effort was carried out to develop general and specialized training programs, to ensure their preparation for all essential activities involved in their work, such as detection of possible donors, family interviews or other management duties, as well as participation in media (radio, TV, …) to increase people’s awareness about donation and the role of the ONT. [2]

The Spanish National Transplant Organization positioned itself as a service agency, in charge of the logistics involved in organ distribution, management of waiting lists, data analysis, basic statistics and storage and any other action that can contribute to improving the donation and transplantation procedure and ensuring the quality of the program.

The presence of coordinators became a key aspect in the program -without disregarding the importance of the other implemented measures-, and has been proven throughout the years to be a determinant factor for its outcome, especially when compared to programs developed in other nations. The reason is that coordinators oversee a plethora of crucial aspects of the process.

Coordinators have the ultimate goal of facilitating the possibility of donation and obtaining the maximum number of good quality organs for transplantation, without leaving any detail subjected to improvisation, and always following rigorously all medical, legal and ethical codes. To do so, and before any donor appears, they must be able to efficiently detect and monitor possible donors, as well as prepare all necessary logistics both outside and inside the hospital, to be ready in case organs become available for transplantation. If so, they also need to verify the optimal state of all organs involved. [3]

When a donor is found, they request the family consent for donation, and supervise the legal certification of the dead body, including the reconstruction of the person's visual appearance after the surgical procedure. Afterwards, they guarantee the correct packaging and transport of all organs involved, and on top of all that, they also need to supervise administrative activities, the correct management of resources (economic, legal, ethical, media), training programs, and the quality, safety and transparency of the practice. [4]

The transplantation process can be regarded as a great example of teamwork, as it is the activity that involves the greater percentage of hospital professionals. The role of the coordinator is therefore to lead the team, and make sure each member is ready to act appropriately at any given time or circumstance. Differences in donation and transplantation rates between regions in our country are sometimes explained by changes of coordinators, which underlines their importance in the success of the Spanish model.

3. RENAL TRANSPLANT

The first case of success in kidney transplantation brings us back to 1954, when a team lead by John Merrill and Joseph Murray, Nobel prize laureates in 1991, was able to implant in a 23-year-old the organ coming from his twin brother –so that rejection would be minimized-. Before that, some failed procedures were carried out that resulted in acute rejection, such as the one that took place in Ukraine in 1933 lead by the surgeon Dr. Voronoy. Advancements in the understanding of compatibility issues and development in medications such as cyclosporine allowed more control of rejection, leading to further prosperous surgeries. [5]

In Spain, the first renal transplants were possible in 1965, in Barcelona's Clinic Hospital and Madrid's Fundación Jiménez Diaz. In 2017, a total number of 135,860 transplants were executed worldwide -a 7.2% increase with respect to the previous year, - among those 89,823 correspond to kidney transplantations, and 3,269 were made in Spain-. [6]

3.1 Types of donors

The Spanish legislation considers someone as possible donor if he or she has not expressed direct opposition to the organ extraction procedure while alive.

There are two main types of donors: living and deceased, and among deceased donors we can differentiate two subtypes: heart beating deceased donors and donors after circulatory death (DCD).

Living renal donors are people who altruistically, and meeting all corresponding regulations, decide to give one of their kidney to someone in need. They must meet all legal requirements and clinical procedures, without coercion or economical remuneration, independently of being related or not to the patient, although it usually involves close family members.

On the other hand, deceased donors are individuals who have passed away because of an irreversible brain injury that completely stops their brain activity (heart beating deceased donors) or that have suffered of asystole, that is, their heart has stopped beating (DCD). Asystole can have more direct implications in the state of the kidneys, as the heart is the responsible of permanently perfuse the organs, and any cease of its activities can result in organ damage. This is why it is only acceptable in specific circumstances. [7] Since, we can differentiate four different categories of possible DCD, which were first defined in the 1995 Maastricht Conference. [8]

Currently in Spain the classification used is the "Modified Maastricht Classification", stablished in Madrid in 2011 [9]:

I. Victims of a sudden death outside the hospital setting and that have not received any resuscitation maneuvers.

II. People who have suffered a cardiac arrest, in or outside a hospital setting, and have received resuscitation maneuvers without success.

III. Individuals that have been clinically diagnosed to suffer from cardiac death shortly, and are withdrawn of life-sustaining therapies.

IV. Individuals with brain death who experience a cardiac stop just before being moved to the surgical room for the organ extraction.

Advancements in transplant coordination have helped introduced this type of donation, which requires higher levels of organization. Until 1999 individuals suffering from asystole were not considered as possible donors in Spain, as it was in that year that type II asystole started to be permitted in our country. However, it was not until 2012 that type II asystole could be implemented. This has allowed donation rates to increase even more during these last years.

Every year more donors from asystole and brain death appear, and this is not only because people become more altruistic regarding organ donation, but because organization and coordination have improved so much that it is nowadays possible to detect donors and obtain more organs in a much more efficient way. The introduction of asystole donors is a clear example of this success, and it can be shown for example with the fact that a significant number of donors from previous years used to appear after car accidents and crashes, and, even if the number of car accidents and death has significantly decreased over the last years, the number of heart beating deceased donors has not decreased. [10]

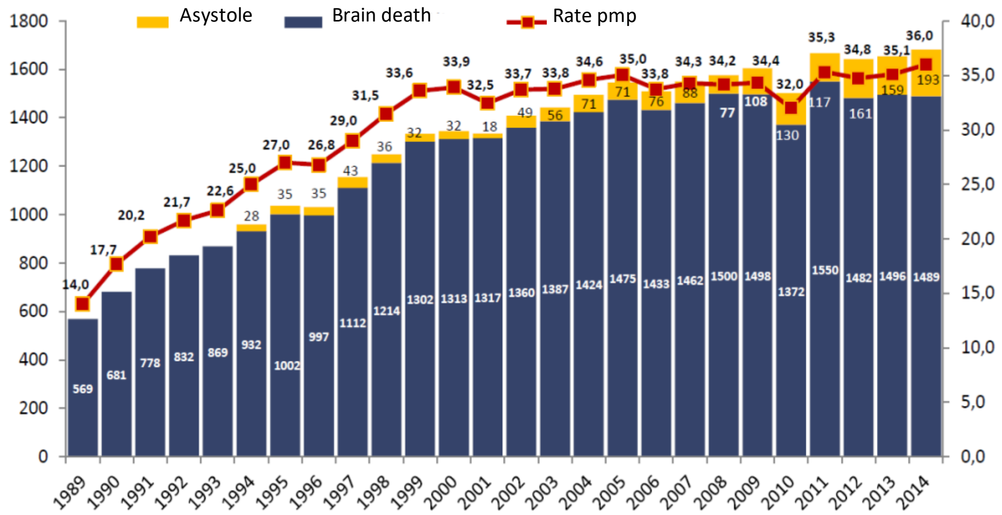


Fig. 3.1 Evolution of each type of donation in Spain from 1989 to 2014

Although there are no actual age limits for donation, recommendations state that donors should be 75-years-old or less, and without clinical history of any renal disease. For asystole, the recommended maximum considered age is 50. However, general health condition is an essential aspect, as it is always possible to find 30-years-old donors in worst health condition than some of 70 or older. For that reason, it is important to assess possible donors in an individual manner, to confirm that there are no other health conditions that can affect the final state of the organ. [11]

3.2 Hospitals with neurosurgical activities

There is an important difference as well between hospitals that perform neurosurgeries and those that do not in terms of number of donors. In hospitals that do have a neurosurgery unit, there are more patients with neurological injury that require critical care, and therefore more donors from brain death because of complications during the surgical procedures.

In the year 1999, the Spanish National Transplant Organization started a program to ensure the optimal quality of all the activities. This program started by analyzing the total number of deaths that occurred in the Intensive Care Unit (ICU), and among those, the number of brain deaths. The ultimate objective of the analysis was to estimate the number of donors that a certain hospital should have in function of other variables such as their number of beds. 85% of all hospital with transplantation extraction activities participated in the analysis, and the examined data showed that 13% of all deaths in hospitals with neurosurgical activities were brain deaths – and possible donors-, whereas this percentage lowered to 5% for hospitals that did not had such activities. Currently in Spain, approximately 55% of all hospitals with extraction capabilities have neurosurgical units. [12]

3.3 Surgical procedure, possible complications and packaging

The surgical and packaging procedures are now standardized and a common kidney extraction consists of many different steps, among which we can distinguish the exsanguination (with or without cannulation), clamping, the introduction of heparin to avoid coagulation, perfusion, preservation liquid to maintain kidney's function and structure and extraction. Although the steps are general indications, the degree of expertise of each surgeon can largely affect the overall result of the extraction. Thus, some complications can take place, including arterial or venous thrombosis and stenosis.

Regarding possible complications after the extraction, there are three main phases in which the removed kidney could suffer important damage. The first one is called warm ischemia time, and refers to the amount of time that passes between the interruption of blood circulation across the organ and its perfusion with a hypothermal preservation solution. The second one is the cold ischemia time, considered as the time between the storage of the organ and its eventual transplant in the receptor. During this cold ischemia time, kidneys are stored in a fridge under hypothermal conditions and with preservation liquids to minimize the energy requirements of the organ. In order to reduce the energy consumption and lessen damage to the kidney, the organ should be stored at a temperature of around 4ºC, but not much less because it could freeze and become unusable as a result. [13]

This is achieved by storing the kidneys in different containers and fridges, to ensure the maintenance of appropriate hypothermal conditions. Each kidney is placed in a sterilized and isolated bag containing preservation liquid. Each bag is then placed inside an opaque container called Duchess (in Spanish, 'Duquesa'), which is filled with a saline solution at a temperature of 5ºC. The Duchess is subsequently placed in another sealed bag, and the ensemble is introduced, in a vertical position and surrounded by ice, inside a portable fridge. [14]

Keeping the kidney cold at 4-5ºC allows it to be optimally stored for a maximum period of around 24 hours before implantation. However, this could also have adverse effects, as it can provoke cellular edema (undesirable excessive fluid volumes accumulated in the circulatory system or interstitial spaces), and accumulation of toxic metabolites.

The third process that can seriously damage the organ is the re-perfusion, once the kidney is implanted and blood circulation is re-established. Blood flux could then provide oxygen but also remove toxic metabolites, which could in turn damage other tissues.

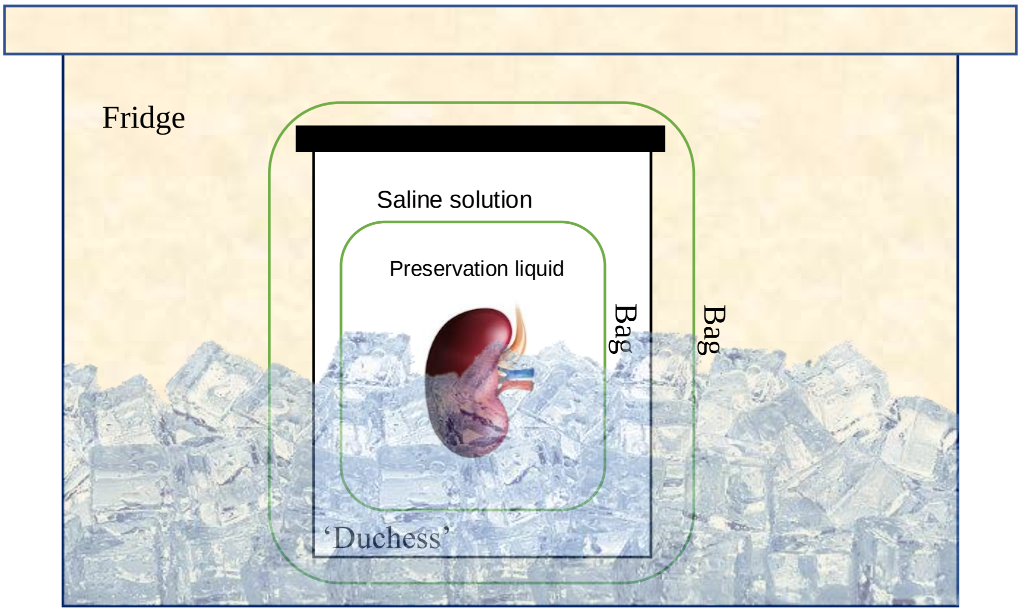


Fig. 3.2 Diagram representing how kidneys are stored

Because the locations of donors and receptors of an organ are not always near, kidneys need to be perfectly stored to ensure that, no matter what the destination is, they are impeccable both functionally and structurally. Even though in general the transplant is performed in the same autonomous community where the extraction took place, that can still involve big transport hours in large regions– such as Andalucía-; also, the organs could only be found compatible with patients from other regions.

In the specific case of La Rioja, this situation is even more present, as the novel program requires the continuous transport of organs to and from the Basque Country. This is the reason why appropriate monitorization and surveillance of both cold ischemia time and temperature inside the fridge should be carried out.

3.4 Monitoring after transplantation. Indicators of optimal organ function and condition

The monitoring of transplanted organs can be differentiated into two main stages. The first one corresponds to the supervising of the first two months after the surgery (short-term) and the other corresponds to the long-term surveillance.

The short-term monitoring can be divided as well into other three periods: the first day, days 2 to 8 and days 9 to 60 after the transplant. The first day, the patients need to be evaluated immediately after leaving the operating room, to check hemodynamic and ventilatory stability and ensure that all immunosuppression protocols have been implemented. In addition, it is important to see whether the patient presents any hemorrhage and, of course, the state of the urine output. During the first week, the patient usually improves its general condition and renal function begins to become more stable. The treatment that he or she must receive is dependent on the state of the transplanted kidney, as these usually show an excellent, slow or retarded function. In this case, urine output is used as a reliable indicator of such function, and more specifically, the serum creatinine levels are observed. [11]

So, given that the most important indicators taken into consideration are the creatinine levels and the volume of urine output, a classification can be established, as the patients with excellent organ function have a rapid decrease in serum creatinine levels and no dialysis is required, whereas those with slow function have a slow decrease in serum creatinine levels and no dialysis required, and the ones with retarded function usually need dialysis and present oliguria. In the latter cases, it could be useful to obtain some images to exclude the possibility of having urine leaks and obstructions.

In all cases, rejection of the graft is an important factor to consider, and can occur immediately after the transplant or some days after. The rejection takes place because of the action of antibodies against donor human leukocyte antigens, recognized as foreign. It is anticipated before, by histocompatibility analysis and in order to recognize if a certain organ is suitable for the patient, and after the procedure, with immunosuppressive treatment; however, there could be situations where it could happen, so it cannot be disregarded. [15]

After the start of the second week, the patients begin or not to be discharged, depending on their condition and some external issues that need to be evaluated as well, such as distance from their homes to the hospital in case of an emergency. Patients are appropriately informed before leaving the hospital facilities of their treatment and condition, and are expected to continue with the indicated medication and diet. Also, they are informed of the possible implications and risks if they fail to follow the advice given.

Lastly, a long-term evaluation needs to be carried out. In the case of the Transplant Coordination Unit of the San Pedro Hospital of La Rioja, where this project was developed, the patients were evaluated six months after the surgery, and then every year after it. In this period, blood tests and checkups are performed, to analyze the presence of any abnormalities. The immunosuppression can have negative effects in the long term leading to further prevalence of infections, so it is important to review periodically the condition of the transplanted individuals. [16]

4. THE AUTONOMOUS COMMUNITY OF LA RIOJA. THE COOPERATION AGREEMENT WITH THE BASQUE COUNTRY

4.1 The Autonomous Community of La Rioja

The Autonomous Community and province of La Rioja is a region located in the North of Spain and surrounded by the Basque Country, Aragon, Navarra and Castile and León. Its total population in 2016 was of about 315,794 people, according to the Spanish National Statistics Institute, becoming the smallest region of Spain in terms of population and one of the smallest in terms of total surface in kilometers squared. [17]

La Rioja has only one public hospital endorsed to extract and transplant organs, the San Pedro Hospital in Logroño, La Rioja's capital, which extracts and transplants kidneys and livers, and has no neurosurgical unit nor activities. It is composed of 630 beds and has 14 available operating rooms. The Transplant Coordination Unit of La Rioja, lead by Dr. Fernando Martínez Soba, is located close to the Intensive Care Unit of such hospital. [18]

Despite being such a small region and with limited resources, La Rioja has become a reference in terms of organ transplant coordination. In 2017, La Rioja was ranked second in kidney donation rates with 71 per million population, and that same year, the average age of donors in La Rioja was 70.7, becoming the region with the oldest donors in Spain. [19]

Ever since 2006, La Rioja has participated in collaborative projects with the Spanish National Transplant Organization in national and international training programs.

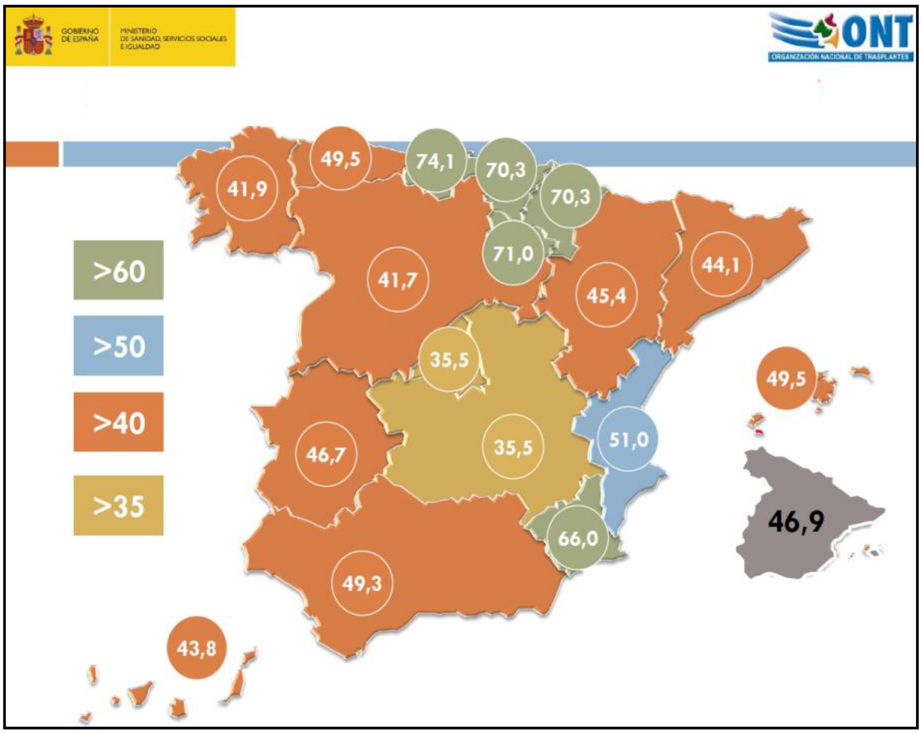


Fig. 4.1 Organ donations in Spain in 2017 per million population *[19]*

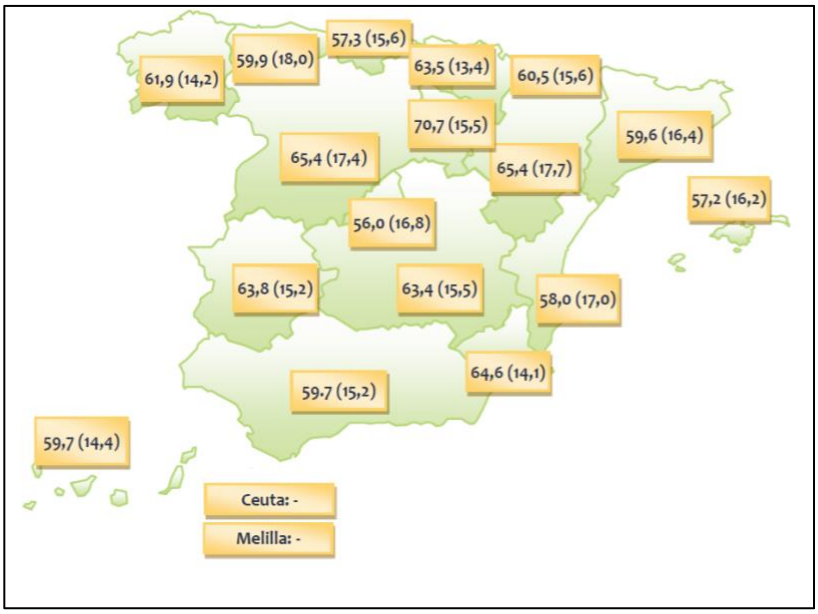


Fig. 4.2 Average Spanish donor age per Autonomous Community in 2017 (national average was 60.4 years) [19]

4.2 Renal Transplant Cooperation Agreement between La Rioja and the Basque Country

Before the year 1995, all renal transplants involving patients from La Rioja were performed in either Zaragoza or Pamplona. However, since the year 1995 a collaboration agreement with the Basque Country (which was officially approved in 1996 in the Congress of Deputies) made it possible for people from La Rioja to be transplanted in Barakaldo's Cruces Hospital. This agreement, always supervised by a monitoring commission, lasted for 15 years, until La Rioja received official sanitary permission to carry out renal transplantation procedures in the San Pedro Hospital of Logroño.

Nonetheless, the process to obtain such permission was complicated, mainly because of national and regional regulatory issues. To begin with, in order to obtain it La Rioja needed legal approval from its own Regional Health Department, and all sanitary authorizations had to follow the legal requisites given by the 2070/1999 Royal Decree that was applicable at that moment. [20] To fulfil those, in the year 2007 the San Pedro Hospital started a training program to prepare professionals that would be involved in transplantation procedures and equipped its facilities with histocompatibility and pathological anatomy laboratories.

Yet, not only there were legal requirements to follow, but also compulsory guidelines validated and accepted by all autonomous communities through the National Transplant Committee, in charge of establishing the criteria for organ distribution.

Before 2011, these criteria specified that the organs had to be first offered to donors located in the same hospital where they were extracted, then to near hospitals in the region or autonomous community and finally to the adjoining autonomous communities. La Rioja wanted to maintain the collaboration agreement with the Basque Country, and for that purpose they had to suggest changing such criteria, so that their kidneys could be offered directly to the Basque Country. These changes in distribution norms were eventually approved in 2010, and led to the writing of a new agreement with law status between the Basque Country and La Rioja, signed in 2011. [21]

Through this agreement both regions agreed to share a common waiting list, so all kidneys coming from La Rioja and the Basque Country would be offered in a shared database, and after La Rioja had already been granted permission for implantation activities, they could be transplanted in either autonomous community.

All these documents were signed right in the middle of an economic crisis, and some political and social sectors began to question the affordability of the program due to its high cost. In 2012, the Spanish National Government pressured the National Transplant Organization to find ways to cut costs and regulate the number of authorized transplantation centers. To do so, the National Transplant Organization released a report analyzing certain epidemiologic variables, with a conclusion stating the recommendation of having one transplantation center for every 1.5 million population, and carrying out in each of them a minimum of 40 transplants per year, unless a lower activity could be justified because of geographical reasons. [22]

A planning criteria for all Spanish transplant programs was released in December 2012, specifying recommendations based on activities and population. La Rioja, because of being the smallest autonomous community in terms of population and performing a low number of surgical procedures, did not satisfy any of the two conditions; nevertheless, its program could continue as it was understood that there was a geographical criterion of enough importance for the activities to be resumed.

In 2013, the agreement between La Rioja and the Basque Country was further extended, including a shared waiting list not only for adults but also for children and living adult kidney transplants. In addition, it was decided in such document that the urgent neurosurgery service of La Rioja would be provided by the one from the Santiago Apostol Hospital in Vitoria.

As of 2018 the program is still successfully underway, with both La Rioja and the Basque Country occupying the top positions in terms of renal donation and transplantation rates in Spain. In addition, it has allowed both regions to reduce the overall waiting list, below the national average. [23]

In September of that same year La Rioja completed its 100th transplant since the beginning of the joint program.

5. DATA. DEFINITIONS

100 kidney transplants were carried out in La Rioja since 2011 as part of the cooperation agreement with the Basque Country. Therefore, the information available corresponds to each of the recipients and the donors from those 100 procedures.

The total number of variables extracted for the donors and for the recipients are defined as follows:

5.1 Donor data

A donor can be referred as a person who, willingly or with family´s consent after passing away, donates an organ that is eventually transplanted. The person can donate organs while still alive (living donor) or after death (deceased donor). In the case of the data that was obtained for the elaboration of this project, it is important to note that there were only deceased donors.

5.1.1 Age: time the donor lived until the organ/s were extracted. In the data, this variable is expressed in years.

5.1.2 Sex: biological distinction of humans into two categories, male and female.

5.1.3 Blood type: description of the donor type of blood. There are four main groups for the ABO system (A, B, AB and O), which differ in the presence of antigens on red blood cells and the antibodies present in plasma. Additionally, the Rh system adds a positive or negative symbol to the ABO system, depending on the presence or not of the Rh antigen on red blood cells. This results in eight possible combinations: A+, A-, B+, B-, AB+, AB-, O+, O-.

5.1.4 Hypertension: the blood pressure is the force that blood exerts over arterial vessel walls as it is pumped by the heart. The measurement is composed of two values, one referring to the systolic (in the moment of a heart beat) pressure and another referring to diastolic (at relaxation). Ideal blood pressure falls in the range of 90/60 to 120/80 mmHg. In the data, a person is categorized as hypertensive if the value of systolic blood pressure is superior or equal to 140 mmHg and/or the diastolic pressure is superior or equal to 90 mmHg.

5.1.5 Diabetes mellitus: disease caused by the inability of the body cells to correctly absorb glucose from the bloodstream. There are two types of diabetes mellitus: type I, in which the body is unable to produce the required amount of insulin (a hormone produced in the pancreas that regulates glucose levels in blood), and type II, in which there is not a lack in production of insulin, but there is a resistance to it, so glucose cannot be correctly absorbed and its concentration in blood increases. In the obtained data, people are simply categorized as diabetic or non-diabetic, without making any distinctions between type I and type II diabetes.

5.1.6 Body mass index: defined as donor body mass (expressed in Kg) over height (expressed in meters) squared.

5.1.7 Donor type: donors can be living or deceased. Given that all donors from the program were deceased, the distinction made is whether this occurred after brain death or circulatory death (DCD). In the region of La Rioja, only type II and type III DCD are considered.

5.1.8 Serum creatinine: waste product produced from creatine degradation. It is present in blood and excreted through urine after kidney filtration. It is usually measured in a concentration of milligrams over deciliters (mg/dL). A normal creatinine concentration range for an adult male individual is between 0.7 and 1.3 mg/dL, while a normal range for an adult female is between 0.5 and 1.2 mg/dL. An increase in creatinine concentration in blood (and therefore, decrease in glomerular filtration rate) can indicate kidney failure, which is the reason why this variable, calculated with blood extraction analysis, is extensively used to determine the state of the donor kidneys. [24]

5.1.9 Glomerular filtration rate (GFR): estimation of the amount of fluid that is filtered from the glomeruli to the Bowman capsule in a nephron (functional unit of the kidney) per minute. It is used to estimate the functional state of kidneys to be donated. The threshold for normal renal functioning is usually established at 60 mL/min, although GFR is calculated taking into account different variables, such as age, sex or race, so the optimal value can vary depending on those. In this project, the calculation of GFR is made using the CKD-EPI (Chronic Disease Epidemiology Collaboration) equation [25]:

CDK-EPI equation for GFR estimation

$$GFR = 141 \times \min\left(\frac{Creat}{k}, 1\right)^{a} \times \max\left(\frac{Creat}{k}, 1\right)^{-1.209} \times 0.993^{Age} \times 1.018[if\ female] \times 1.159\ [if\ black] \quad (5.1)$$

Where: *Creat = Creatinine [mg/dL]*
k = 0.7 if female; k = 0.9 if male
a = -0.329 if female; a = -0.411 if male

5.1.10 Hepatitis C virus: virus responsible of liver inflammation. It can also have negative effects on kidneys, so it was important to check if the donor is a carrier of the virus to assess the state of his or her kidneys. None of the donors participating in the program had the virus.

5.1.11 Hospital of origin: the hospital in which the donor organs were extracted. Since the program is based on a close collaboration between La Rioja and Basque Country, the majority of organs were originated in those regions. In La Rioja, the main hospital is the San Pedro Hospital, located in Logroño, while in Basque Country the principal ones are located in Vitoria, Bilbao and San Sebastián. Other hospitals that generated kidneys that participated in the program are in Galdakao, Madrid, Catalonia, Asturias or Navarra. If a region produces an organ in a certain location and a compatible recipient cannot be found in that region, the organ is offered to other ones. That is the reason why some of the organs that participated in the analysis came from outside the collaborating regions.

5.2 Recipient data

A recipient is a person who gets transplanted an organ (in this case a kidney) coming from a donor. The recipient is first diagnosed with a chronic renal disease and is included in a waiting list. Since a malfunctioning kidney cannot appropriately filter toxic products present in blood, the person has to undergo dialysis (artificial filtration) until a suitable donor is available. In order to determine suitability, several factors are taken into account, and among those it is of tremendous importance the human antigen leukocyte (HLA) match between the donor and recipient. All recipients from the program were residents of municipalities in La Rioja.

5.2.1 Age: time the recipient lived until the graft was implanted (expressed in years).

5.2.2 Sex: whether the recipient was male or female.

5.2.3 Blood type: recipient blood group type out of the eight possible combinations.

5.2.4 Hypertension: if the value of the recipient's systolic blood pressure was superior or equal to 140 mmHg and/or diastolic pressure was superior or equal to 90 mmHg before the surgical procedure.

5.2.5 Diabetes mellitus: if the patient was diagnosed with diabetes before the date of the transplantation procedure.

5.2.6 Body mass index: recipient's body mass (expressed in Kg) over height (expressed in meters) squared.

5.2.7 Time in waiting list: amount of time (in days) that each patient had to wait before the date of the procedure, after being introduced in the waiting list (a database that collects and orders by date of introduction of the information from the patients waiting to receive a kidney transplantation). The final order of patients receiving the kidney does not necessarily coincide with the order of waiting list because of compatibility and suitability issues.

5.2.8 Time in dialysis: amount of time that a patient spends in dialysis after being diagnosed with a chronic renal disease and until she or he undergoes the surgical procedure to receive a kidney, even if this one fails and the patient needs to go back to dialysis immediately after.

5.2.9 Number of previous transplants: for each patient, the number of kidney transplantation procedures that were performed prior to the date of the one described.

5.2.10 Race: a distinction was made between black and non-black recipients, as people of black race have been associated with lower graft survival. [26] In this program, no recipient was Black.

5.2.11 Serum creatinine: as previously mentioned, creatinine is a waste product present in blood and excreted through urine. It is a good indicator of kidney function, as it is necessary for the calculation of the glomerular filtration rate, to estimate if kidneys are functioning correctly. Since patients are in dialysis before the transplant, creatinine values prior to the transplant date have no important meaning. Therefore, the creatinine values analyzed are those obtained after the procedure. More specifically, creatinine values were extracted for each patient at the date of hospital discharge, one month, six months, and every year after the surgery. All creatinine values for most of the patients were not available; for circumstances that are not under the hospital control, some recipients did not take the blood tests that they were recommended to take at the indicated dates, so there was missing information for the majority of them.

It is important to note that because of the issue explained above, the only value that was available for all recipients was the one corresponding to the date of hospital discharge. Although that variable was not ideal for analysis, as it is not a fixed amount of time (while some patients were discharged some days after the procedure, for others it took several weeks to be sufficiently recovered to abandon the hospital facilities), it was the only one that could be used for all patients.

5.2.12 Glomerular filtration rate (GFR): amount of fluid filtered from the glomeruli per minute. The GFR value can give an estimation the optimal function of the implanted kidney. It was calculated for each creatinine value available and making use of the CDK-EPI equation (see 5.1.9)

5.2.13 Transplantation date: date (day, month and year) in which the recipient underwent the operation.

5.2.14 Failure of the graft: if the transplanted kidney failed after the surgery. This failure can be classified as early (within one year of the surgery) or late (occurring after more than a year since the date of the procedure). There were 11 kidneys that failed out of the 100 that were analyzed, and among those 7 suffered from early failure, caused mainly by arterial/venous thrombosis or septic shock, and the other 4 suffered from late failure, due to acute rejection or advance chronic kidney disease. In those cases, besides looking at the reason of failure, the restarting date of dialysis was also obtained.

5.2.15 Date of death: information regarding the date of death of the recipients that passed away since the start of the program in 2011 (a total of 7 individuals). There were no cases of death directly caused by the surgery of the transplants.

5.2.16 Cold ischemia time: amount of time that passes from the moment the organ is stored for preservation, after being extracted from the donor, to the moment it is transplanted in the recipient. Storing the organ in hypothermal conditions minimizes its energy requirements, and numerous studies have provided recommendations on the maximum number of hours that kidneys can be stored in such conditions in order not to decrease significantly its functionality, which is currently considered as 24h. [27] As it has been previously mentioned in section 3.3, the organ can suffer significant damage when stored and in the process of re-perfusion, and the total number of hours that it is preserve outside the body and the conditions in which such preservation occurs are of vital importance and need to be carefully examined.

5.2.17 HLA Compatibility: Human Leukocyte Agents (HLA) are proteins on the surface of white blood cells and other body tissues involved in immune recognition and able to identify foreign particles that could damage the body. So, the risk of acute rejection of the transplanted kidney is therefore affected by the disparity in these proteins between the donor and the recipient. HLA proteins can be divided in two main classes (class I and class II). Class I includes HLA-A, HLA-B and HLA-C, whereas class II contains HLA-DR, HLA-DQ and HLA-DP. A crossmatch test is necessary for all donors and recipients to avoid the possibility of graft rejection in the patient; however, the advancement in immunosuppressant drugs administered to the patients allows some degree of mismatching. [28]

6. DESCRIPTION OF THE DATA

All the available analyzed data was obtained through access to the database of La Rioja Health Department, maintaining the privacy of each individual involved in the transplantation program. This extraction was tedious, as the information for each patient required to be searched and analyzed through the San Pedro Hospital information systems. It was required to spend at least 30 minutes to collect all the important information for each individual, and collaboration from the transplant coordinators - Dr. Martínez Soba and Dr. Calleja- was indispensable, not only to collect and help with guidance to learn how to navigate through the portal, but also to review the reports of some individuals and assess if any other medical conditions were important to mention.

6.1 Description of recipients' data

As mentioned before, there were 100 procedures in the San Pedro Hospital between 2011 and September 2018, and out of those procedures, there were 98 recipients – two patients received two kidneys, each at different procedures - and 100 donors. In addition, 15 patients had already received one or more kidney transplants before the one received in this period of time (13 had received one transplant and 2 people had received two).

Some of the recipients were born in countries such as Pakistan, Argentina or Armenia, among others. In the following table the origin of the patients of each transplant is shown. It is important to keep in mind that the number of recipients from Spain and Brazil in the table is 85 and 2 respectively, since the nationality is computed for each transplant and disregarding the fact that there are two repeated patients; those two patients are originally from Spain and Brazil, so the actual number of patients born in those two countries would be 84 and 1. This issue affects as well the other variables discussed because the information for each transplant is analyzed individually and without considering that two patients had two implants.

With respect to the sex of these recipients, 27% of the patients were females and 73% were male, and the average age was 54.12. In this case, there were no important differences between the average age for the females (53.59), and the average age of the males (54.31).

TABLE 6.1. PLACE OF BIRTH OF THE 100 RECIPIENTS

Place of birth	**Number of patients**
Spain	85
Pakistan	5
Argentina	2
Brazil	2
Armenia	1
Colombia	1
Italy	1
Morocco	1
Peru	1
Rumania	1

The percentage of patients suffering from hypertension was of 95%, and 17 recipients suffered from diabetes (3 had type II diabetes). The average waiting list time was 436.82 days, and it took on average 1676.6 days to receive the implant since the beginning of dialysis. In 24 out of the 100 surgeries the implanted kidney was the left one.

TABLE 6.2 SUMMARY OF RECIPIENTS' INFORMATION

Sex	Male: 73%	
	Female: 27%	
Hypertension	Yes: 95%	
	No: 5%	
Diabetes Mellitus	Type I: 14%	
	Type II: 3%	
Blood Group (as indicated in the database)	A	4%
	A+	34%
	A-	6%
	B+	3%
	B-	5%
	AB	1%
	AB+	2%
	AB-	1%
	O	4%
	O+	32%
	O-	8%

Average waiting list time	436,82 days
Average time since the beginning of dialysis until surgery	1676.6 days
Implanted kidney	Left: 24%
	Right: 76%

Regarding grafts survival, it is essential to mention that 11% implanted kidneys during the course of the program were non-functioning. There were different reasons why the kidney stopped functioning, and a distinction could be made between the ones that failed because of complications during surgery and those that failed because of the patient's condition (an advanced chronic renal condition or an acute rejection of the implant).

Out of the 11 implants that failed, 7 were caused by early surgical complications, while the other four were unsuccessful more than a year after the date of the operation. The personnel from the surgical team suffered changes and substitutions during these years, having a direct impact on the outcome of some transplants. Furthermore, it is important to keep in mind that the Hospital only received 100 organs in 7 years (a little bit more than 14 organs per year), so the inexperience of the team added to those changes in personnel seem a reasonable explanation for such situation. This number is expected to decrease in the future because of the experience that the surgeons are obtaining.

During this time between 2011 and 2018, 8% of the recipients died, but no one did as a direct result of the surgical procedure. Though, it is worth mentioning that 5 out of those 8 patients passed away with a functioning implanted kidney; the rest passed away with non-functional kidneys.

TABLE 6.3 TOTAL DEATHS OF RECIPIENTS BETWEEN 2011 AND 2018

Total deaths = 8	Deaths with functioning kidney = 5
	Deaths with non-functioning kidney = 3

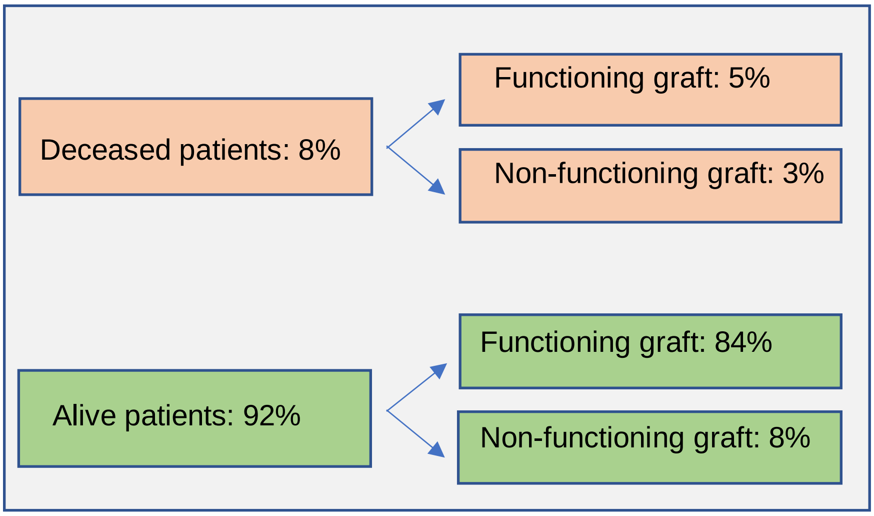


Fig. 6.1 Graft survival diagram from the 100 studied patients

6.2 Description of donor's data

There was a total of 100 different donors, coming from La Rioja, the Basque Country and other regions: Catalonia, Asturias, Cantabria, Madrid and Navarra. The accessibility to the donors data was still very restricted due to privacy issues, and all acquired information was obtained from the reports sent by the transplant coordination of the hospitals of origin to the San Pedro Hospital Transplant coordinators. These reports included information about the donor's age, sex, blood group, hypertension, diabetes and creatinine levels before the extraction, as well as the origin of the implant, the cause of the death and the HLA compatibility matches.

The average age of all donors was of 56.93 years. A differentiation could be made between the organs coming from La Rioja, Basque Country and other regions, resulting in average donor age of 59.76, 56.39 and 58.88 for each. 44 out of the 100 donors were females, 27% were hypertensive, and 8% were diabetic (no distinction between type I and type II was noted). Regarding the height and weight, the averages were 167.36 cm and 73.85 Kg, whereas the mean creatinine levels were 0.7505 mg/dl, inside the optimal range. At the national level, in 2017 60% of kidney donors were males, 20% were diabetic and 50% were hypertensive. [23]

TABLE 6.4 NUMBER OF ORGANS FROM EACH REGION

REGION OF ORIGIN	CITY	NUMBER OF ORGANS
La Rioja	Logroño	13
Basque Country	Barakaldo	22
	Bilbao	9
	San Sebastián	32
	Vitoria	14
	Galdakao	1
Madrid	Madrid	2
Asturias	Oviedo	2
Cantabria	Santander	2
Catalonia	Barcelona	1
	Badalona	1
Navarra	Pamplona	1

Another fundamental variable extracted was the cause of death. As previously discussed and explained, a classification was made to distinguish between heart beating or non- heart beating (asystole) deceased donors. In the San Pedro Hospital only type II and type III asystole are performed.

The number of donors from brain death and asystole are shown in the following table. Brain death represented the 73.76% of total donor deceases in Spain in 2017.

TABLE 6.5 *NUMBER OF DONORS PER TYPE*

Brain death donors = 82	
Asystole donors = 18	Type II asystole = 5
	Type III asystole = 13

TABLE 6.6 SUMMARY OF DONOR'S INFORMATION

Sex	Male: 56%	
	Female: 44%	
Hypertension	Yes: 27%	
	No: 73%	
Diabetes Mellitus	Yes: 8%	
	No: 92%	
Blood Group (as indicated in the reports)	A+	38%
	A-	8%
	B+	3%
	B-	1%
	AB	1%
	O+	39%
	O-	10%
Average creatinine levels	0.7505 mg/dl	
Average height	167.36 cm	
Average weight	73.85 Kg	

Other relevant collected information included the HLA compatibility mismatches and cold ischemia times for each organ. As it has already been explained, HLA compatibility is major factor to consider in order to avoid graft rejection and immunological responses. The following table shows the number of organs depending on the number of total mismatches between the donor and the recipient (HLA-A, HLA-B and HLA-DR have each two alleles, so the maximum global number of mismatches equals six).

TABLE 6.7 NUMBER OF ORGANS ACCORDING TO THE GLOBAL NUMBER OF MISMATCHES

Number of mismatches	Number of organs with such number of mismatches
0	1
1	2
2	11
3	39
4	34
5	13
6	0

The cold ischemia time measurement is essential to understand the state of the organ while stored and transported to La Rioja and its eventual function after implantation. The maximum number of hours that the organ should be stored is usually established at 48, but, as discussed, optimal maximum time is set at 24h [29]. It should be noted that there were seven organs that exceeded 24h of cold ischemia time, 50 grafts experienced a cold ischemia time of 20 to 24 hours, and the other 43 kidneys had a cold ischemia time of 20 hours or less.

For the analyzed 100 cases, the average cold ischemia time was 20.45 hours, and the median was 20.8 hours.

TABLE 6.8 NUMBER OF ORGANS FOR EACH COLD ISCHEMIA TIME RANGE

Cold ischemia time (hours)	Number of organs with cold ischemia time in that range
Ischemia >= 24	7
20 < ischemia > 24	50
Ischemia <= 20	43

7. ANALYSIS OF OUTCOMES

To do all statistical analysis, some programming was required, and it was executed using the following software: The R Project for Statistical Analysis (R).

7.1 Origin and distribution of the grafts

The total number of recipients reviewed in the project equaled 100. Out of those 100 patients, the organ that each patient received was obtained from one of the following hospitals:

TABLE 7.1 REGION OF ORIGIN OF THE KIDNEYS

REGION OF ORIGIN	CITY	HOSPITAL
La Rioja	Logroño	Hospital San Pedro
Basque Country	Barakaldo	Hospital Universitario de Cruces
	Bilbao	Hospital Universitario Basurto
	San Sebastián	Hospital Universitario Donostia
	Vitoria	Hospital Santiago Apóstol
	Galdakao	Hospital Universitario de Galdakao
Madrid	Madrid	Hospital Universitario Doce de Octubre
		Hospital Universitario La Paz
Asturias	Oviedo	Hospital Universitario Central de Asturias
Cantabria	Santander	Hospital Universitario Marqués de Valdecilla
Catalonia	Barcelona	Hospital Clinic de Barcelona
	Badalona	Hospital Municipal de Badalona
Navarra	Pamplona	Hospital de Navarra

Even though the program that started in 2011 implied a close collaboration between La Rioja and the Basque Country, some of the recipients received an organ originated in other regions. Once a hospital is able to extract an organ from a donor, it is first offered to the region of that hospital or the region with which the hospital has an agreement, following the order of their waiting list. If in the region there is not a patient that can meet the compatibility or suitability requirements, the organ is offered to other locations where someone can receive it. This is the reason why some of the transplanted kidneys originated in more than the two regions (Basque Country and La Rioja) that participate in the collaborative program that is analyzed in this project.

For that reason, a distinction between the region of origin was made, so that the outcome of the transplants could be analyzed based on the location of extraction. The organs extracted in La Rioja were labeled as “1”, while the ones from the Basque Country were labeled as “2”. All other regions were grouped together as “3”.

TABLE 7.2 CLASSIFICATION BASED ON THE REGION OF ORIGIN

REGION NUMBER	REGION OF ORIGIN	CITY
1	La Rioja	Logroño
2	Basque Country	Barakaldo
		Bilbao
		San Sebastián
		Vitoria
		Galdakao
3	Madrid	Madrid
	Asturias	Oviedo
	Cantabria	Santander
	Catalonia	Barcelona
		Badalona
	Navarra	Pamplona

The program approved in 2011 between La Rioja and the Basque Country established a shared waiting list for both regions. Nevertheless, La Rioja is smaller in terms of population size and number of donors. So, the first required analysis was to prove that the distribution of the obtained kidneys was being fair for both regions. For that matter, current populations for both La Rioja and Basque Country were obtained from the internet [17]:

TABLE 7.3 POPULATION OF LA RIOJA AND THE BASQUE COUNTRY

REGION	POPULATION
LA RIOJA	315,794
BASQUE COUNTRY	2,171,131

The ratio of La Rioja population was then calculated:

$$Ratio\ population = \frac{Rioja}{Rioja + Basque\ Country} = \frac{315{,}794}{315{,}794 + 2{,}171{,}131} = 0.127$$

Basque Country: population of Basque Country
Rioja: population of La Rioja

For the program, out of the 100 patients studied, the distribution according to the region of origin of the organ was as follows:

TABLE 7.4 NUMBER OF ORGANS FOR EACH REGION NUMBER

REGION OF ORIGIN	REGION NUMBER	RECIPIENTS (TOTAL = 100)
LA RIOJA	1	13
BASQUE COUNTRY	2	78
OTHER	3	9

Since the collaborative program was established between La Rioja and the Basque Country, those recipients who received a kidney from the region labeled as ‘Other’ were disregarded for this analysis.

The proportion of recipients of a kidney from La Rioja was then calculated:

$$Proportion = \frac{RLR}{RBC + RLR} = \frac{13}{78 + 13} = 0.143$$

RBC: Recipients of organ from the Basque Country
RLR: Recipients of organ from La Rioja

After those calculations, a test of Test of Equal or Given Proportions was run on R, making use of the prop.test function. The Test of Proportions is used to analyze whether a certain population proportion equals another population proportion. [30] The established null hypothesis is that both proportions are equal and the alternate hypothesis is that they are different. For a level of significance of 0.05, a p-value smaller than the level of significance would imply that the null hypothesis need to be rejected, and so, the two population proportions would be different. The obtained result is shown below:

Null hypothesis	H_0: $p_1=p_2$
Alternate hypothesis	H_1: $p_1 \neq p_2$

```
#  H0: p = ratioPopulation
#  H1: p ~= ratioPopulation

p = proportion
prop.test(x = 13, n = 91, p = ratioPopulation)
```

```
        1-sample proportions test with continuity correction

data:  13 out of 91, null probability ratioPopulation
X-squared = 0.09, df = 1, p-value = 0.8
alternative hypothesis: true p is not equal to 0.127
95 percent confidence interval:
 0.0812 0.2355
sample estimates:
    p
0.143
```

Fig. 7.1 Proportion test for the populations and organ donation of La Rioja and the Basque Country

Before analyzing the results, it is important to define what the p-value is. The p-value is the smallest level of significance for which the obtained sample would require rejecting the null hypothesis. It refers to the probability of obtaining a result that is less compatible with the null hypothesis than the result obtained with the sample. A p-value smaller than the fixed level of significance (in this project, always 0.05), implies lack of support to the null hypothesis (H_o), and so it must be rejected. A p-value larger than the fixed level of significance implies that support to the null hypothesis is enough not to reject it. [31]

In this case, as the p-value equaled 0.8, we could not reject the null hypothesis, and therefore could not reject that the distribution of kidneys had been fair for both La Rioja and the Basque Country. It is important to mention that because the total number of organs was small, the 95% confidence interval obtained was very broad.

7.2 Analysis of the outcome of each transplant based on the origin of the graft

In order to assess the success of the transplants, GFR was calculated for each patient, and the values were used to find possible relationships between success of the procedure and origin of the organ.

7% of the implants did not correctly function as a consequence of the surgical procedure (because of intrarenal, arterial and venous thrombosis). Since the outcome of those grafts was directly affected by the operation, they were disregarded during the following analyses; the other 93 transplants were then the ones evaluated.

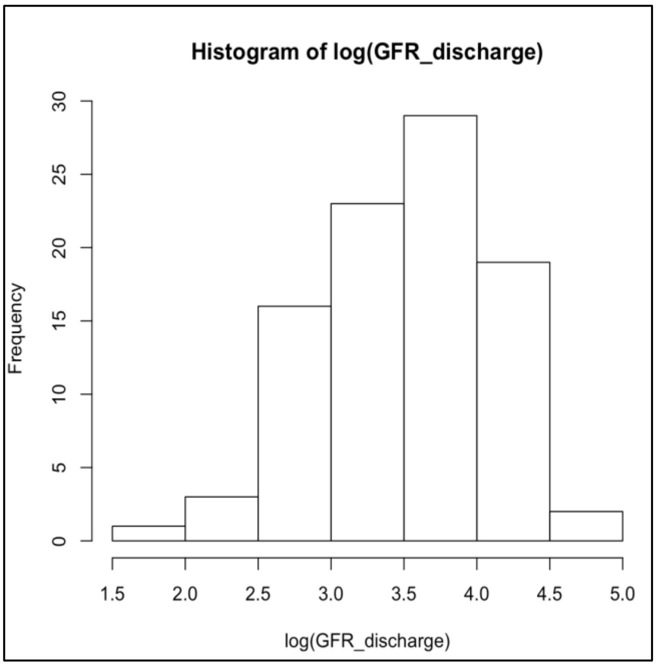
The values of GFR were calculated following the CDK-EPI equation (5.1.9). This equation considers the age, sex, race and creatinine values for each patient. Race was disregarded for these calculations, as none of the patients analyzed were Black, and the creatinine value used corresponded to that of date of hospital discharge, since it is the only one that was available for all the studied individuals. After plotting the histogram, right skewness was observed, so natural logarithms were taken for normalizing the obtained data, as there is enough evidence to consider that the whole population follows a normal distribution, something that cannot be observed from the available data because there is still renal failure after the procedure in the vast majority of the cases. So, renal function was measured as the natural logarithm of GFR.

A normal distribution can be defined as a continuous variable probability distribution that is used to represent random variables with unknown distribution. Its density function graph is a symmetric and bell-shaped curve, with height and width dependent on the population variance. The larger the variance (that is, the larger is the dispersion) the shorter and wider is the curve. [32]

In the case of the available data, values of Glomerular Filtration Rate could not be considered as a normal since most of patients had renal dysfunctions. However, it would have been a normal distribution if the totality of the population was considered. In order to perform test such as the Analysis of Variance (ANOVA), a normal distribution is a requirement, so the data needed to be normalized. [33]

It has been previously mentioned that an optimal value of GFR was considered to be approximately 60 mL/min; however, this value needs to be put in context, as each individual requires personal analysis. For instance, the optimal GFR value for a male with age bigger than 60 is different than the one for a 30-year-old male, and the optimal value of GFR for that 60-year-old male is different than the one for a 60-year-old female. In this case, for people that have recently undergone surgery to receive a kidney, a value of 60 mL/min is not common, especially at the date of hospital discharge. A positive evolution of the transplant would involve an increasing value of GFR over time, but this value may or may not rise above the 60 mL/min threshold even though the patient's condition improves.

After taking natural logarithms, the following histogram was obtained:



log (60) = 4.09

Fig. 7.2 Histogram for the logarithm of Glomerular Filtration Rate at the date of hospital discharge

Boxplots of the obtained date according to the region of origin were then represented, where region 1 corresponds to La Rioja, region 2 corresponds to the Basque Country and region 3 groups all other locations.

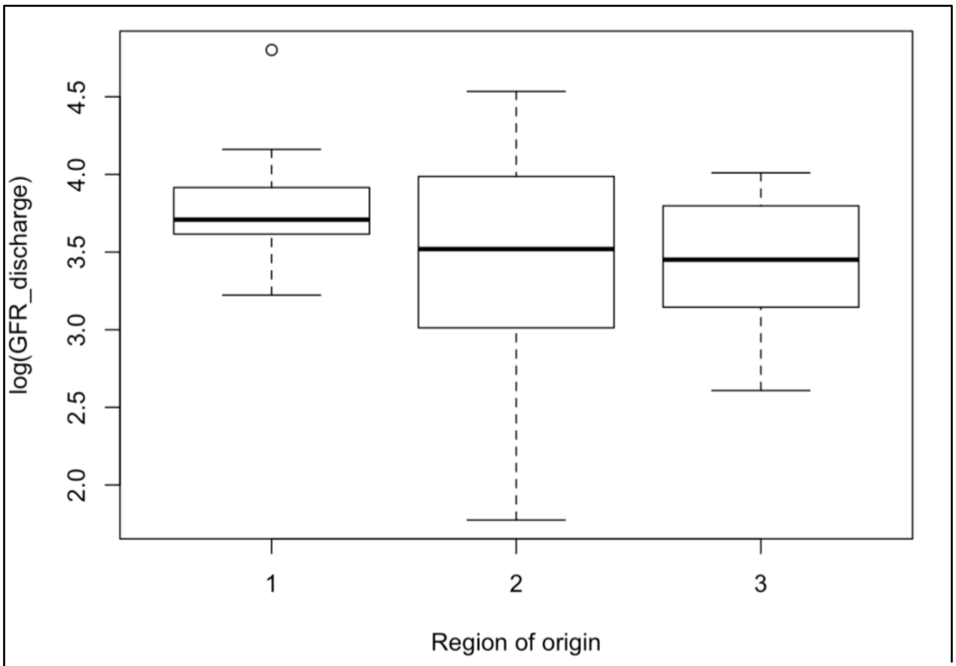


Fig. 7.3 Boxplots of the log(GFR) at the date of hospital discharge according to the region of origin

At first glance, it could look like the kidneys from La Rioja (region 1) had higher value of GFR, and therefore better function. In order to assess the veracity of such statement, an ANOVA test was carried out.

The ANOVA (Analysis of Variance) test examines the possibility of having equal means for two or more populations. Nonetheless, certain conditions need to be satisfied in order to use it. Firstly, there has to be independence between the samples; secondly, data needs to present homoscedasticity (homogeneity of variance); and lastly, data needs to present normal distribution, which was not the case. It allows to compare different populations, establishing the null hypothesis that the populations are equal and the alternate hypothesis that at least one of them is different to the others. [34]

Null hypothesis H_0: $\mu_1=\mu_2=\ldots=\mu_n$

Alternate hypothesis H_1: $\mu_j=\mu_i$ $j=1, 2,\ldots,n$

Then, in order to normalize the data to perform the ANOVA test, a Box-Cox transformation was applied. The Box-Cox transformation consists on using a *lambda* value to transform the dependent variable (in our case the GFR at the time of hospital discharge) to obtain a linear model.

The Box-Cox transformation can be completely defined as a power transformation used to transform non-normally distributed dependent variables into a normally distributed set. To do so, a lambda (λ) value is calculated and used to calculate the new values of the variable. The lambda value is obtained with a log-likelihood procedure. [35]

$$X.new = \frac{(X.old^{\lambda} - 1)}{\lambda}$$

This is the code used to extract the boxplots for the transformed data according to the region of origin:

```
Box = boxcox(GFR_discharge ~ Region_Origin, # Transform GFR as a single vector
             lambda = seq(-6,6,0.1))      # Try values -6 to 6 by 0.1
Cox = data.frame(Box$x, Box$y) # Create a data frame with the results
Cox2 = Cox[with(Cox, order(-Cox$Box.y)),] # Order the new data frame by decreasing y
Cox2[1,] # Display the lambda with the greatest value
lambda = Cox2[1, "Box.x"]
GFR_discharge_box = (GFR_discharge ^ lambda - 1)/lambda

boxplot(GFR_discharge_box ~ Region_Origin,
        ylab="BoxCox-transformed GFR_discharge",
        xlab="Region of origin", main = "Boxplots of transformed GFR at the date
        of hospital discharge according to the region of origin")
```

Fig. 7.4 Script used for data transformation

Obtaining the following figure:

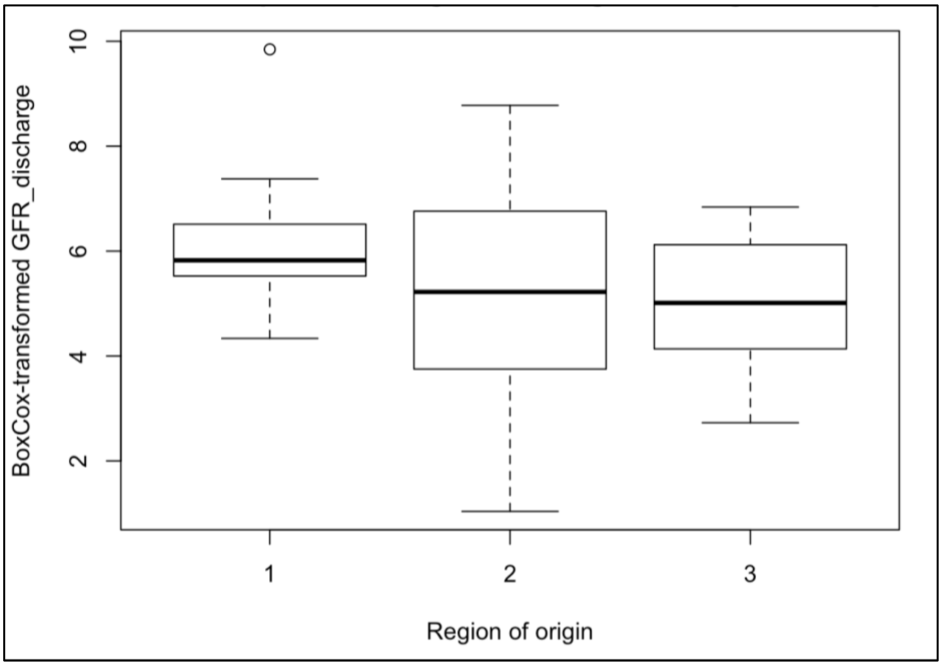


Fig. 7.5 Boxplots of transformed GFR at the date of hospital discharge according to the region of origin

Once the data was normalized, the ANOVA test was run with the following piece of code:

```
Anova_GFR_Origin <- aov(GFR_discharge_box ~ Region_Origin)
summary(Anova_GFR_Origin)
```

```
              Df Sum Sq Mean Sq F value Pr(>F)
Region_Origin  1      8    8.00    2.61   0.11
Residuals     91    279    3.07
```

Fig. 7.6 Script and result obtained for the ANOVA test

As the p-value obtained equaled 0.11 (bigger than 0.05), it could not be concluded that there were significant differences between the GFR means of the three populations.

7.3 Analysis of the outcome of each transplant based on the distance of the hospital of origin to Logroño

Even though the analysis by regions was found to be non-significant, a more in-depth analysis was required. The objective in this case was to analyze the functionality of the transplanted kidneys (again, using the GFR value at the date of hospital discharge) against the distance that the graft traveled before being implanted in the recipient.

To do so, the first step consisted on finding on the internet the distances from each of the hospitals to the San Pedro Hospital, where the transplantation procedures always took place. The Google Maps tool was used [36], and road distances were considered.

The following table was created:

TABLE 7.5 DISTANCE FROM THE HOSPITAL OF ORIGIN TO THE SAN PEDRO HOSPITAL

CITY	HOSPITAL	**DISTANCE TO SAN PEDRO HOSPITAL (km)**
Logroño	Hospital San Pedro	0
Barakaldo	Hospital Universitario de Cruces	144
Bilbao	Hospital Universitario Basurto	139
San Sebastián	Hospital Universitario Donostia	164
Vitoria	Hospital Santiago Apóstol	68
Galdakao	Hospital Universitario de Galdakao	139
Madrid	Hospital Universitario Doce de Octubre	331
	Hospital Universitario La Paz	327
Oviedo	Hospital Universitario Central de Asturias	420
Santander	Hospital Universitario Marqués de Valdecilla	234
Barcelona	Hospital Clinic de Barcelona	470
Badalona	Hospital Municipal de Badalona	482
Pamplona	Hospital de Navarra	51

Data was then normalized, using the Box-Cox transformation, and a linear regression was calculated with R. A linear regression model tries to model a relationship between two variables. To do so, the studied data is fitted into a linear equation:

$$y = a + bx \tag{7.2}$$

In such equation, the variable *x* is considered the explanatory variable, while the variable *y* is the dependent variable. Constant *a* represents the intercept with the y axis, and *b* is the value of the slope of the line. [37]

Once a linear regression is applied, the p-value (probability value) indicates the level of significance of the model. A p-value smaller than 0.05 would indicate that there is a significant relationship between the explanatory and the dependent variables.

To check that the data was correctly transformed and that it followed a normal distribution after applying the Cox-Box transformation, the residuals' histogram was reviewed. A residual can be defined as the difference between the observed and the predicted value for each point, and the histogram of the residuals for a linear regression model should show a normal distribution to assess the normalization of the data.

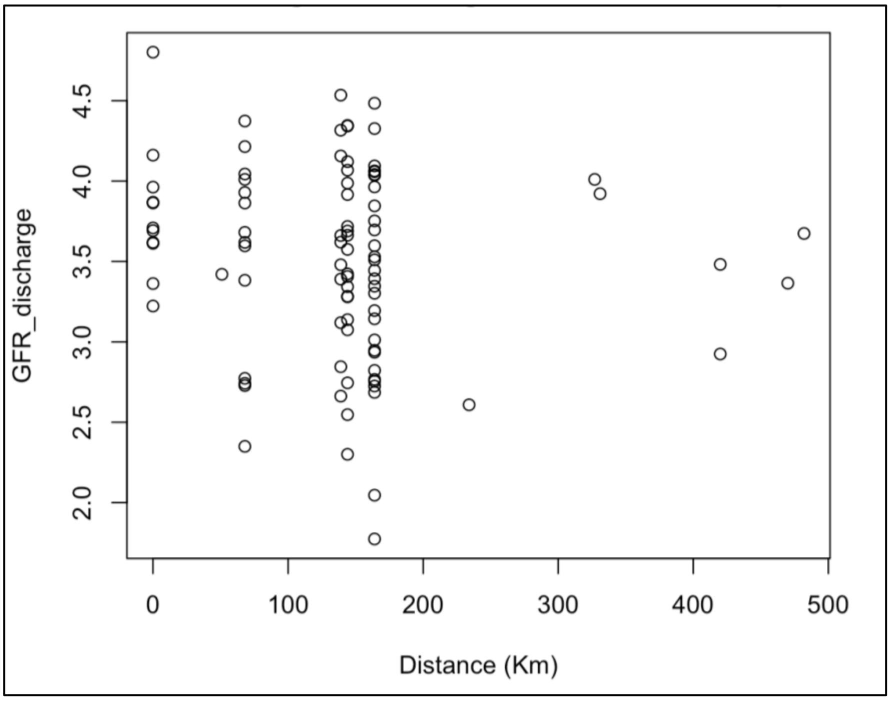


Fig. 7.7 Graph representing GFR at the date of discharge depending on the distance from the origin of the organ to San Pedro Hospital

The result of the regression can be observed in the following figure:

```
lm(formula = GFR_box_dis ~ Distance)

Residuals:
   Min     1Q Median     3Q    Max
-4.199 -1.192  0.048  1.355  4.184

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  5.66214    0.33142    17.1   <2e-16 ***
Distance    -0.00259    0.00200    -1.3      0.2
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.76 on 91 degrees of freedom
Multiple R-squared:  0.0182,	Adjusted R-squared:  0.00741
F-statistic: 1.69 on 1 and 91 DF,  p-value: 0.197
```

Fig. 7.8 Linear regression model for the normalized GFR and the distance to San Pedro Hospital

As it can be observed, the p-value obtained equaled 0.197, so it could not be concluded that there was a significant relationship between distance and organ function. The conclusion was not exactly the same when the analysis was conducted exclusively for the two participating regions in the collaborative program (in that case, p-value obtained was 0.0716). That p-value was not smaller than 0.05, so no strict relationship could be established, but it was closer than the previous one, which would indicate that the organs whose origin was the Basque Country had worse outcomes at the time of hospital discharge than those from La Rioja.

```
lm(formula = GFR_box_dis ~ Distance_Rioja_BC)

Residuals:
   Min     1Q Median     3Q    Max 
-4.013 -1.254 -0.108  1.300  3.770 

Coefficients:
                  Estimate Std. Error t value Pr(>|t|)    
(Intercept)        6.07601    0.45184   13.45   <2e-16 ***
Distance_Rioja_BC -0.00625    0.00342   -1.83    0.072 .  
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.78 on 83 degrees of freedom
Multiple R-squared:  0.0386,	Adjusted R-squared:  0.027 
F-statistic: 3.33 on 1 and 83 DF,  p-value: 0.0716
```

Fig. 7.9 Linear regression model for the normalized GFR and the distance to San Pedro Hospital, only considering the regions of La Rioja and the Basque Country

7.4 Analysis of the outcome of each transplant based on KDRI

In the year 2009, professors from the University of Michigan and Ohio State University elaborated an index to assess the life expectancy of deceased donor kidneys, the Kidney Donor Risk Index (KDRI). [38] The objective of the KDRI is to estimate quantitatively the survival time of kidneys based exclusively on donor and transplant parameters.

Using data obtained from the Scientific Registry of Transplant Recipients and analyzing the importance of different donor parameters, the researchers developed a prediction equation able to give an estimated value of graft survival (the lower the value of the KDRI obtained, the higher the expected survival of the graft).

The donor parameters taken into account for such prediction equation were the following: age, height, weight, race of the donor, creatinine value before the organ extraction, hypertension, diabetes or presence of Hepatitis C virus in the donor, and the cause of death (cerebrovascular accident or donation after cardiac death); on the other hand, the transplant parameters analyzed were: HLA mismatches between donor and recipient (HLA-B and HLA-DR) and cold ischemia time for each transplant. In addition, the equation includes information regarding the number of organs involved in the transplantation (block transplantation or double kidney transplant), which are not considered in this case, since none of the patients were transplanted from the program in such conditions.

For the analysis, a reference donor was established. This reference donor was a 40-year-old non-African race person, with a height of 170 cm, weight of 80 kg, non-diabetic, non-hypertensive brain dead donor with hepatitis C virus negative, and with a serum creatinine of 1 mg/dL; in addition, two HLA-B mismatches and one HLA-DR mismatches were considered, as well as a cold ischemia time of 20 hours.

The resulting KDRI prediction equation was:

$$\begin{aligned}\text{KDRI} = \text{Exp}(&-0.0194 \times I\,[\text{age} < 18\text{ yr}] \times [\text{age} - 18\text{ yr}] + 0.0128 \times [\text{age} - 40\text{ yr}] \\ &+ 0.0107 \times I\,[\text{age} > 50\text{ yr}] \times [\text{age} - 50\text{ yr}] + 0.179 \times I\,[\text{race} = \text{African American}] \\ &+ 0.126 \times I\,[\text{hypertensive}] + 0.130 \times I\,[\text{diabetic}] + 0.220 \times [\text{serum creatinine} - 1\text{ mg/dL}] \\ &- 0.209 \times I\,[\text{serum creatinine} > 1.5\text{ mg/dL}] \times [\text{serum creatinine} - 1.5\text{ mg/dL}] \\ &+ 0.0881 \times I\,[\text{cause of death} = \text{cerebrovascular accident}] - 0.0464 \times [\{\text{height} - 170\text{cm}\}/10] \\ &- 0.0199 \times I\,[\text{weight} < 80\text{kg}] \times [\{\text{weight} - 80\text{kg}\}/5] + 0.133 \times I\,[\text{donation after cardiac death}] \\ &+ 0.240 \times I\,[\text{hepatitis C positive}] - 0.0766 \times I\,[\text{HLA-B mismatch} = 0] - 0.0610 \times I\,[\text{HLA-B mismatch} = 1] \\ &- 0.130 \times I\,[\text{HLA-DR mismatch} = 0] + 0.0765 \times I\,[\text{HLA-DR mismatch} = 2] + 0.00548 \times [\text{cold ischemia time} - 20\text{ hr}] \\ &- 0.364 \times I[\text{en bloc transplant}] - 0.148 \times I\,[\text{double kidney transplant}])\end{aligned} \tag{7.3}$$

where I (A) is set to 1 if condition A is applies to the donor kidney of interest (i.e., if the donor kidney of interest possesses condition A), and otherwise it is set to 0.

Making use of this equation and the available donor data, a linear regression model was calculated to check for a possible relationship between GFR and KDRI values. This could imply that the Kidney Donor Risk Index can be applied to our data as a predictor of kidney function post-transplantation.

The Box-Cox transformation model was again used to normalize the data and the regression model was created:

```
Call:
lm(formula = GFR_dis_box_KDRI ~ KDRI)

Residuals:
   Min     1Q Median     3Q    Max 
-3.986 -1.424  0.149  1.292  4.169 

Coefficients:
            Estimate Std. Error t value Pr(>|t|)    
(Intercept)    6.325      0.582   10.87   <2e-16 ***
KDRI          -0.634      0.343   -1.85    0.068 .  
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.74 on 91 degrees of freedom
Multiple R-squared:  0.0362,	Adjusted R-squared:  0.0256 
F-statistic: 3.42 on 1 and 91 DF,  p-value: 0.0678
```

Fig. 7.10 Linear regression model for the normalized GFR and Kidney Donor Risk Index (KDRI)

The p-value obtained in this case equaled 0.0678. This value would technically implicate that there is no significant relationship between the GFR and KDRI variables (as p-value > 0.05). However, it is worth mentioning that it is located near the edge of being significant. Therefore, it could be assumed that the KDRI can be an indicator of good organ function for the analyzed data.

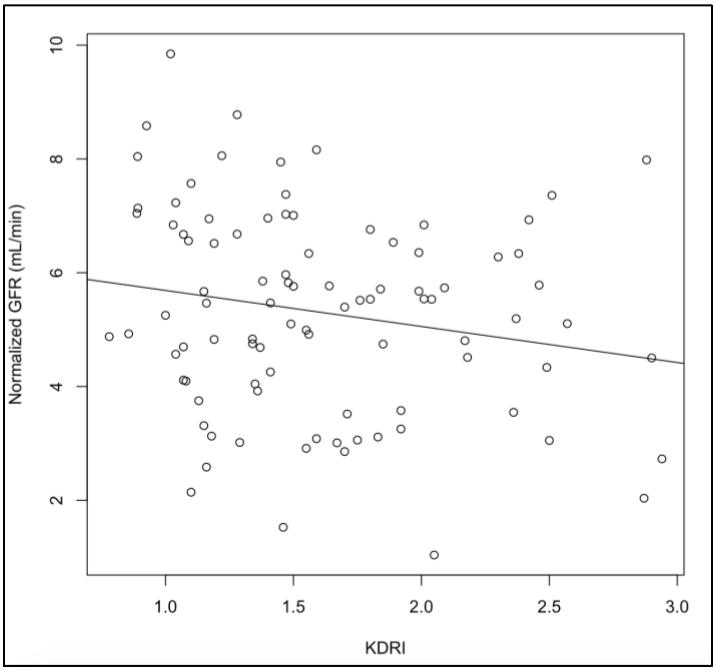


Fig. 7.11 Linear regression model graph for normalized GFR and KDRI

To continue, a similar examination was made but using two explanatory variables (KDRI and Distance). The normalization was made using the Box-Cox transformation, but considering the two explanatory variables, and they were included as well in the regression model.

```
lm(formula = GFR_alta_box_KDRI_and_distancia ~ KDRI + Distance)

Residuals:
   Min     1Q Median     3Q    Max 
-3.935 -1.237  0.104  1.358  3.849 

Coefficients:
            Estimate Std. Error t value Pr(>|t|)    
(Intercept)  6.62116    0.62930   10.52   <2e-16 ***
KDRI        -0.61177    0.34279   -1.78    0.078 .  
Distance    -0.00240    0.00198   -1.22    0.227    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.74 on 90 degrees of freedom
Multiple R-squared:  0.0518,	Adjusted R-squared:  0.0307 
F-statistic: 2.46 on 2 and 90 DF,  p-value: 0.0915
```

Fig. 7.12 Linear regression model for the normalized GFR and two explanatory variables (KDRI and distance to San Pedro Hospital)

The joint p-value obtained (0.0915) revealed no relevant significance, and it could be observed directly the importance of the Kidney Donor Risk Index over the Distance.

7.5 Analysis of the outcome of each transplant based on cold ischemia time

Cold ischemia time can be defined as the number of hours that passes since the kidney is preserved to the moment it is transplanted on the recipient. Information on the cold ischemia time preceding the transplantation procedure was collected by the Transplant Coordination of La Rioja at the San Pedro Hospital, and was provided for analysis.

The aim in this case was to find a possible relationship between the GFR value at the date of hospital discharge and cold ischemia time. The Box-Cox transformation was utilized to normalized the available date, and the regression model was calculated:

```
lm(formula = GFR_dis_box_isch ~ ischemia)

Residuals:
   Min     1Q Median     3Q    Max
-3.045 -1.021 -0.017  0.877  3.352

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)   7.3745     0.9290    7.94  5.1e-12 ***
ischemia     -0.1440     0.0452   -3.19    0.002 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.32 on 91 degrees of freedom
Multiple R-squared:   0.1,      Adjusted R-squared:  0.0905
F-statistic: 10.2 on 1 and 91 DF,  p-value: 0.00198
```

Fig. 7.13 Linear regression model for the normalized GFR and cold ischemia time

The p-value (0.00198 < 0.05) indicated a significant relationship between GFR and cold ischemia time. A longer preservation of the organ therefore implied a lower GFR value at the time of hospital discharge.

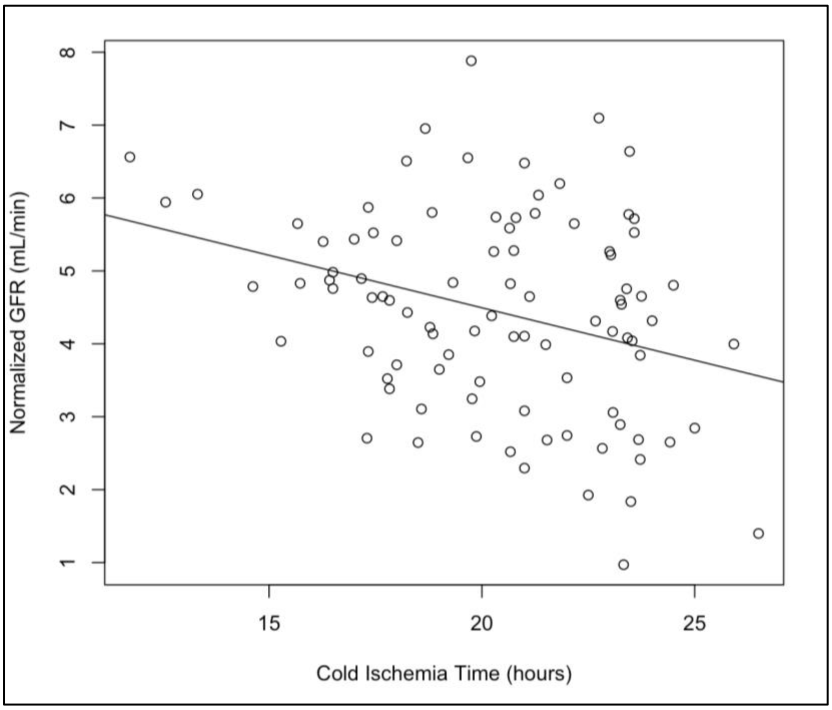


Fig. 7.14 Linear regression model graph for the normalized GFR and cold ischemia time

From this evaluation, it could be extracted that conservation is a key factor to take into account, as cold ischemia time could be interpreted as a predictor of the immediate success of the transplant. Nevertheless, it is important to keep in mind that the GFR value analyzed was the one at the date of hospital discharge, so a lower GFR value at this point does not necessarily imply better performance in the long term.

Moreover, distance could not be considered a predictor of the success because the cold ischemia time for longer distances was found to be smaller. This is due to the fact that the transportation of organs from farther regions is usually completed by plane, reducing the time that the organ remains preserved in the fridge. For instance, the cold ischemia time of the organ transported from Barcelona was found to be shorter (14.6 hours) than all the ones from originated in Vitoria, even though the distance from Catalonia to Logroño is much greater.

Furthermore, the San Pedro Hospital in Logroño lacks resources to proceed with the operation at any time of the day, leading to more cold ischemia hours in case an organ becomes available during the night, since the procedure would take place on the following morning.

Finally, it is important to mention that the KDRI equation considers the value of cold ischemia time for the calculation of the Kidney Donor Risk Index. Since cold ischemia time and GFR were found to have a significant connection, a relation between KDRI and GFR can also be established.

In conclusion, La Rioja and the Basque Country need to reduce cold ischemia times of the organs to improve the functionality of those kidneys once they are transplanted.

7.6 Variation of time of ischemia and GFR depending on the season

The way the organ is transported has a direct effect on the outcome of the transplant, so in order to additionally evaluate the importance of cold ischemia time and the transportation conditions, data was separated into two categories. This was performed with the intention of finding other variables that may affect kidney function through the process.

For that matter patients were separated into two groups: those who received an organ in April, May, June, July, August or September, and those who received it in either October, November, December, January, February or March.

The separation was made based on climatological conditions, as the average temperature in Spain from April to September can be considered as different than the average temperature from October to March, and external environmental conditions can affect the general temperature of the fridge that transports the organ (hotter seasons could raise the temperature above the recommended limits, damaging the organs).

After creating the dichotomous variable *Season* and assigning a value of *1* to the organs transported from October to March -the cold season-, and a value of *2* to those transported from April to September - the hot season-, normalization was applied using the Box-Cox transformation.

The main purpose was to analyze the possible differences of GFR at the date of discharge (that is, kidney function) depending on the season in which the transplant took place. Boxplots were represented for the GFR values corresponding to each season, and a t-test was to compare the means of the two variables was run as follows:

Null hypothesis H_0: $\mu_{cold} = \mu_{hot}$

Alternate hypothesis H_1: $\mu_{cold} \neq \mu_{hot}$

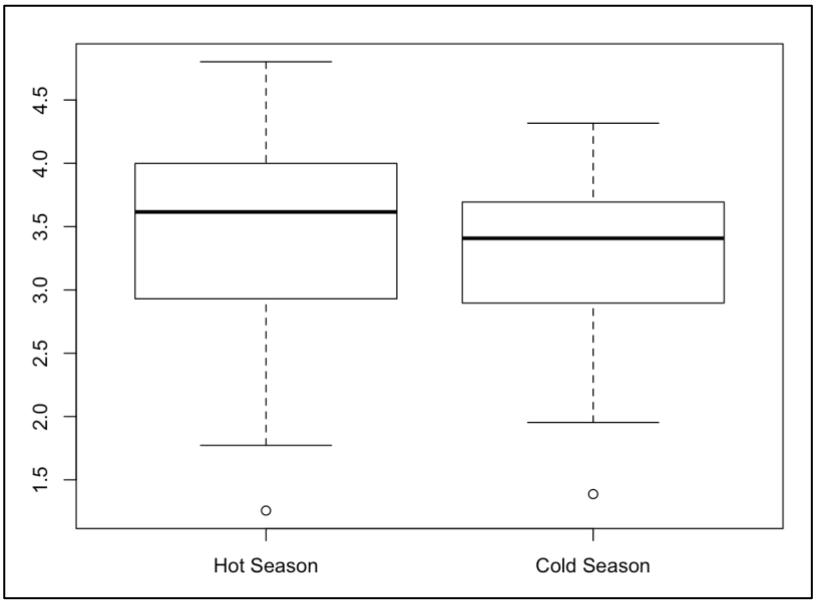


Fig. 7.15 Boxplots of transformed GFR at the date of hospital discharge according to the season

```
> t.test(ColdSeasonBoxGFR, HotSeasonBoxGFR)

	Welch Two Sample t-test

data:  ColdSeasonBoxGFR and HotSeasonBoxGFR
t = -1, df = 100, p-value = 0.2
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -1.829  0.411
sample estimates:
mean of x mean of y
     6.17      6.88
```

Fig. 7.16 T-test script to compare GFR means during hot and cold seasons

The p-value obtained (0.2) indicated that it could not be concluded that there were significant differences in the GFR value depending on the season in which the procedure took place.

In order to analyze the part of the GFR value at the time of discharge that is not explained by the cold ischemia time, the residuals from the GFR ~ ischemia linear model previously created were considered (Fig. 7.13). The aim was to check any difference in the quality of the transplanted organs depending on the season when they were transplanted, but considering equal cold ischemia times for all of them so that it does not influence the obtained results.

Boxplots were represented as well for these residuals, corresponding to each season, and a t-test was to compare the means of the two residual variables was evaluated:

Null hypothesis	H_0:	$\mu_{ResidualsCold} = \mu_{ResidualsHot}$
Alternate hypothesis	H_1:	$\mu_{ResidualsCold} \neq \mu_{ResidualsHot}$

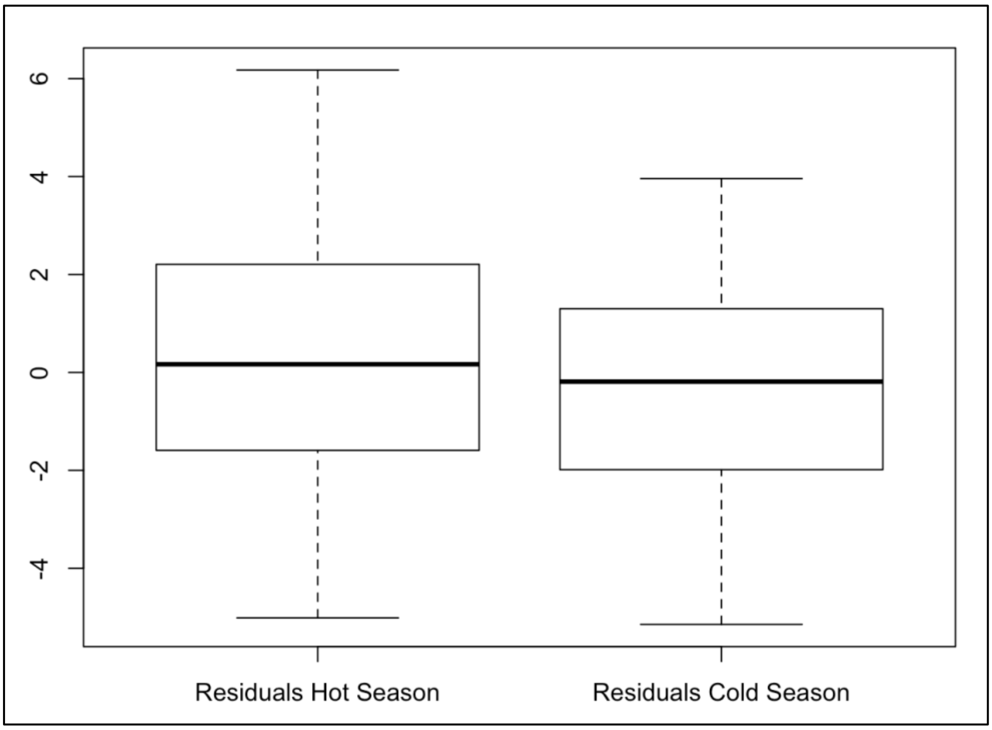


Fig. 7.17 Boxplots of transformed GFR residuals at the date of hospital discharge according to the season

```
> t.test(HotResid,ColdResid)

	Welch Two Sample t-test

data:  HotResid and ColdResid
t = 1, df = 100, p-value = 0.3
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -0.469  1.412
sample estimates:
mean of x mean of y
    0.207    -0.264
```

Fig. 7.18 T-test script to compare GFR residuals means during hot and cold seasons

In this case a p-value of 0.3 was observed, so it could not be concluded that there were significant differences in the procedures depending on the season, especially now that the effects of the cold ischemia times were not taken into account.

8. ANALYSIS OF STORAGE CONDITIONS. EXPERIMENT

To continue with the investigation of the conditions of the organs during the transportation to the San Pedro Hospital in Logroño, it was required to check not only the external climatological conditions, but also the internal ones in the fridge that contains the organs. For that purpose, it was important to collect data regarding the temperature inside the container to confirm that the kidneys were being carried at the appropriate and recommended range of temperatures.

As it has been previously mentioned, the technique to store each kidney is standardized by the National Transplant Organization for all Spanish regions, and involves covering the organ with several layers of bags, with preservation solutions, and a container, surrounded by ice and located inside a conventional fridge, without any motors. This method has a lot advantages, as it is simple and inexpensive, but lacks reliability during the transport as there are no additional instruments to monitor the temperature at every moment to ensure that the organ is stored at the appropriate temperature range (4-5ºC, never below 0ºC to avoid freezing, and never above 5ºC to minimize energy consumption). Even though the method is efficiently designed and appropriately tested, its lack of complexity did not allow to record information on the temperature of each organ that was transplanted to the receptors in La Rioja.

Since no information was available for analysis for the studied cases, a simple experiment was design to test that the temperature conditions were maintained using this packaging method, which consisted on placing a portable thermometer inside the 'Duchess' and monitor for several hours the temperature inside the container, simulating the conditions that any other kidney ready to be transplanted would have. To carry out this experiment the Transplant Coordination Unit of La Rioja, politely and following all legal requirements, asked families if they would accept to donate the kidneys of their deceased relatives for experimental purposes, even if that organ was not in good condition to be donated for transplantation. Those organs were then extracted and stored reproducing the real situation.

To measure the temperature inside the 'Duchess', different possibilities were considered to ensure that certain conditions were satisfied, such as having a device that could be as close as possible to the organ but without incurring in damage to it, waterproof, small enough to fit into the container and that could be monitored from the outside. The solution found was to use a RFID (radio frequency identification) temperature sensor, and given the time constraints to carry out the experiment - as the number of available organs donated for study is low-, the best available devices in the market were searched, and the model LOM16 from the company NEWSTEO Wireless Monitoring® was selected, with the following characteristics [39]:

TABLE 8.1 NEWSTEO WIRELESS MONITORING LOM 16 DEVICE. TECHNICAL CHARACTERISTICS

Size	90mm x 26mm
Weight	26 g (with battery)
Operating temperature range	-40°C … +70°C
Accuracy	± 0.3°C [-30°C…+60°C], ± 1°C beyond
Resolution	0.1°C
Measurement frequency	From 1 measurement per second to 1 measurement every 4 hours
Memory capacity	Up to 32 256 measurements with date and time
Signal range in free field	Up to 200 m
Battery	1/2 AA Lithium Thyionle with connector

Along with the two LOM 16 sensors purchased, an antenna to receive the signals and a software to automatically collect and write the data into a computer were also included.

Fig. 8.1 Materials used: LOM16 RFID sensor, key containing the required software for visualization and receptor antenna

The working mechanism of the experiment consisted on introducing one of the tube-shaped sensors inside a plastic bag, and introducing this bag inside the 'Duchess' and near to the organ, as close as possible but in a way that no damage could not be done to the kidney, even if this one was not going to be used for transplantation purposes. The sensor emitted a radiofrequency that was detected from the outside. The same procedure was applied with another sensor, which was in this case on the outside of the 'Duchess' but inside the fridge, where the ice is usually located. The aim was to detect both temperatures and analyze the differences for each of the experiments carried out with every organ.

A total of four kidneys were donated for the experiment, and the temperature data was collected every 2 minutes. The graph was automatically drawn for each case as well.

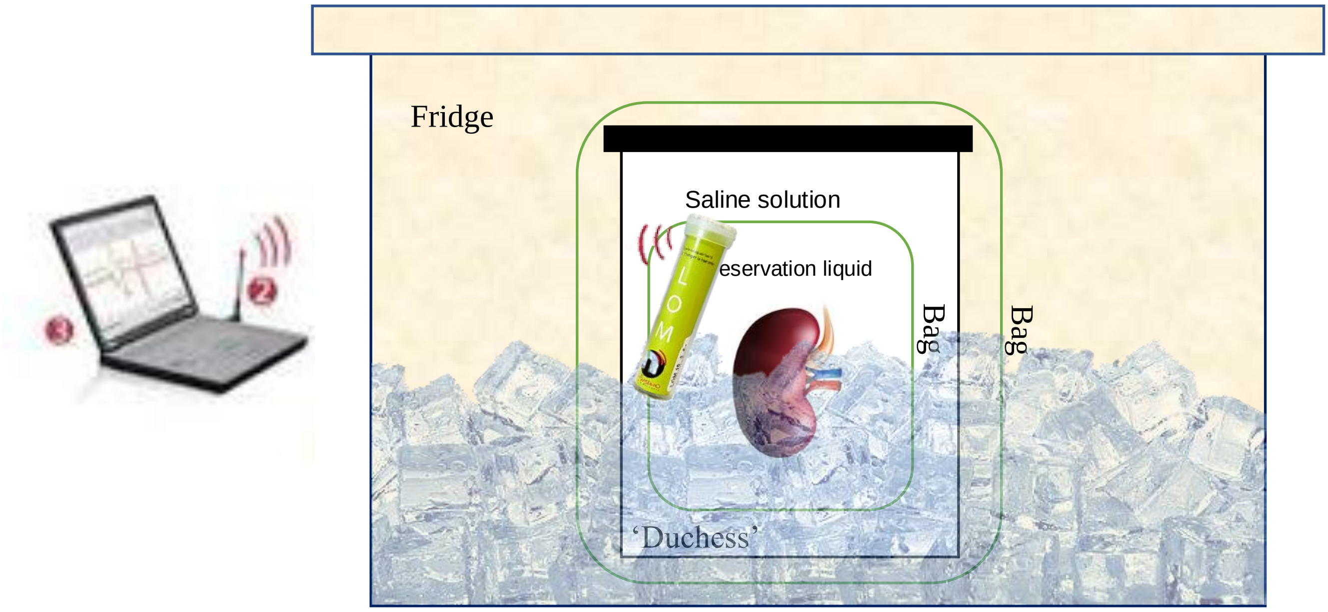
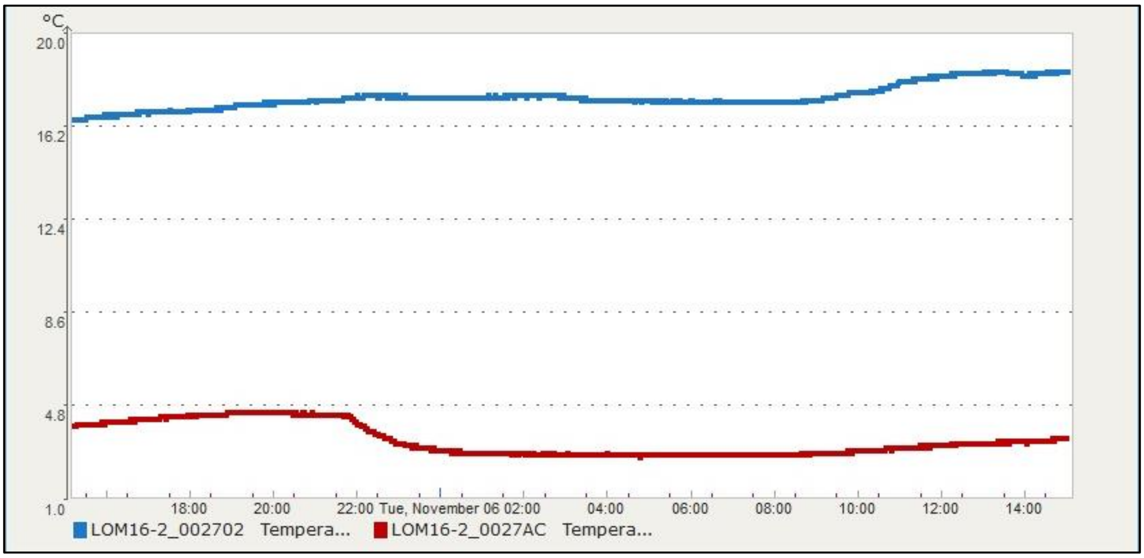


Fig. 8.2 Schematics of the working mechanism

Below are examples of two of the obtained graphs:



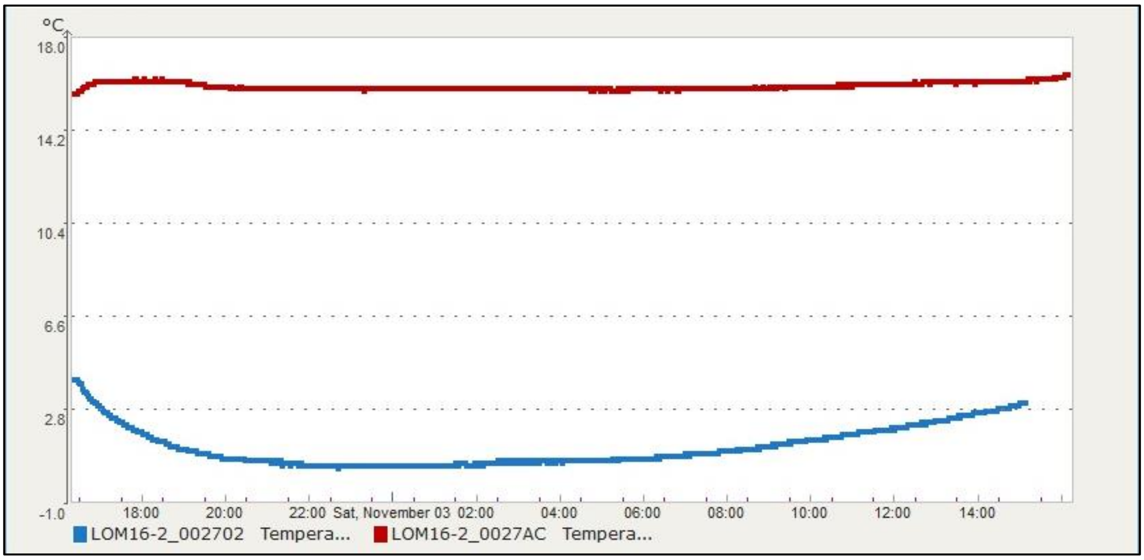


Fig. 8.3 Graphs obtained for the experiments carried out, using two temperature sensors, placed inside and outside the 'Duchess'

As it can be observed, the graphs showed that the temperature is not preserved accurately in the optimal temperature range (ideally 4-5ºC). In contrast, the results showed acceptable, but no great, preservation temperatures between 0ºC and 5ºC, and in some cases alarming temperatures below 0ºC that could cause the organ to freeze.

Although economic and easy to prepare, the storage method was detected to be imprecise. Further and more in-depth analysis will be required to design a better storage technique that can maintain the low-cost and ease of this system.

9. CONCLUSIONS

The renal transplantation program initiated in the year 2011 between La Rioja and the Basque Country has been a success in terms coordination, reducing waiting lists and making donation and transplantation available for a wider population. Despite this accomplishment, that has positioned both La Rioja and the Basque Country on top of the regions with higher donation and transplantation rates in Spain, the analysis presented in this report shows room for enhancement.

In order to improve the glomerular filtration rate value of the patients at the date of hospital discharge, both communities need to work towards reducing cold ischemia times, as longer cold ischemia times have been shown to decrease the functionality of the organs when patients leave the hospital facilities. In addition, efforts need to be placed on improving the storage conditions of the organs to maintain the kidneys in the optimal temperature range, as the current method has been proven to lack precision in that sense.

Lastly, it is important to understand the small amount of operations carried out in the San Pedro Hospital every year when compared to other national hospitals. In that regard, surgeons had less patients to operate and to gain experience, so the learning curve is expected to increase over the future years, which could help avoid some of the early graft failures that took place.

10.SOCIO-ECONOMIC IMPACT

10.1 Research impact

The success Spain has achieved throughout these years regarding transplant coordination, donation and transplantation has been astonishing, becoming an international benchmark and leader in the field. Nonetheless, the National Transplant Organization is continuously examining ways to improve the system even more, and the report here presented aims to contribute to that objective.

Primarily, it is important to mention that it is not common in Spain to complete the analysis performed in this report. Most of the Autonomous Communities do not share the data as in this case, and the fact that this could be done here, with the help of the Transplant Coordination Unit of La Rioja, could stimulate the rest of the Transplant Coordination Units to contribute and aid improving the tremendously efficient system we are fortunate to have in our country.

This project has the ultimate intention of improving the outcomes of patients receiving kidney transplants, and it has been concluded that there are indeed some variables, which could be controlled, that can help for that purpose. The analysis accomplished can therefore have high social implications in the area, especially for those in need of a renal transplant in the future.

Finally, it is worth mentioning how surprising it is for an impressively developed system to keep transporting the organs in such a rudimentary manner. This report could therefore have implications in suggesting the research of other ways that could transport the organs in perfect conditions, as their state is fundamental for the result of the procedures.

10.2 Project costs

The table below summarizes the items used and its costs for the project, along with the costs of personnel and the number of hours that each of them contributed to this activity.

TABLE 10.1 PROJECT COSTS

PROJECT COSTS			
Item	# Units	Cost per unit (€)	Total cost (€)
Refrigerators	2	75	150
Ice (bags of 3 kg)	10	2	20
NEWSTEO Wireless Monitoring LOM16 (2 loggers, software, magnet, batteries)	1	350	350
Personal computer	1	800	800
R project software	1	Free	-
Other software	1	100	100
Round bus trips from Madrid to Logroño	10	30	300
		Subtotal:	**1,720€**

TABLE 10.2 PERSONNEL COSTS

PERSONNEL COSTS			
Subject	# Hours	Cost per hour (€)	Total cost (€)
Student	360 (12 ECTS)	20	7,200
Tutors	100	45	4,500
Surgeons	50	60	3,000
Nurses	50	35	1,750
		Subtotal:	**16,450€**

Then, the approximated total cost was:

TABLE 10.3 TOTAL PROJECT COSTS

CONCEPT	TOTAL COST
PROJECT	1,720 €
PERSONNEL	16,450 €
	18,170 €

Below is a table with the estimated cost of each of the 100 transplants studied in this project, including the procedure, medication and treatment:

TABLE 10.4 ESTIMATED TRANSPLANT COSTS

TRANSPLANT COSTS		
# Transplants	**Estimated cost per transplant (€)**	**Total cost (€)**
100	32,000	3,200,000
	Subtotal:	3,200,000 €

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