

# Organ Transplantation in Argentina

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## DEMOGRAPHICS AND HEALTHCARE OF THE ARGENTINEAN REPUBLIC

Argentina is a federal republic located in the southern portion of South America, with a mainland area of 2780400 km<sup>2</sup>. Argentina is the eighth largest country in the world, and the second largest in Latin America. Spanish is the main language; the population has been estimated at 43847430 in 2016, (Figure 1). The Human Development Index as a statistical composite of life expectancy, education, and per capita income indicators ranks Argentina as 45th worldwide in 2016. Healthcare is provided through a combination of multipayers, including employer and labor union-sponsored plans, government insurance plans and private health insurance providing care through public and private hospitals and clinics. Argentina has reduced its infant mortality from 70 per 1000 live births in 1948, to 12.8 in 2015; life expectancy at birth had been raised from 60 years in 1948, to 76.3 in 2015.

Organ transplantation started in South America in 1957 with the first kidney transplant in Buenos Aires. In 1979, Argentina developed a National Organization to centralize Procurement and Transplant Services, currently called Instituto Nacional Central Unico Coordinador de Ablación e Implante (INCUCAI). INCUCAI is part of the National Ministry of Health and one of the first organizations of its kind in South America.<sup>1</sup>

## STRUCTURE OF TRANSPLANTATION SERVICES

INCUCAI functions as a central organization, coordinating and legalizing all donation and transplant activities and processes.

The country is divided in 5 main procurement regions. There are 133 approved transplanting centers: 55 for kidney, 28 for liver, 22 for heart, 17 for kidney-pancreas, 9 for lung and 2 for intestinal transplantation, with different rates of activity; centers belong both to private (93) and public (40) health systems.

Since 2005, all insurance companies, physicians, patients, and general population have free access to regulations at all steps of transplantation ([www.incucai.gov.ar/SINTRA](http://www.incucai.gov.ar/SINTRA)),<sup>2</sup> providing an entirely transparent process.

By law, presumed consent to donate organs is anticipated, unless registered with the determination not to donate an organ after death. There is a single national waiting list by organ.

Argentina has endorsed the Declaration of Istanbul and actively participated in the Pontifical Academy of Sciences summit on Organ Trafficking and Transplant Tourism.

INCUCAI has been successful in improving deceased donor rates to 11.2 donors pmp in 2017.<sup>2</sup> INCUCAI has also established binational agreements for lung and intestinal listing, procurement, and transplantation with Uruguay.

The Argentinean Transplant Society has been founded in 1982 as a scientific organization for all transplant professionals and allied health related members; it works in closely with the Latin American and Caribbean Transplant Society and The Transplantation Society.

## HEART AND LUNG TRANSPLANTATION

The first lung transplant was performed in 1967 followed by the first heart transplant in 1968<sup>2</sup>; since then, a total of 479 lung transplants have been performed (average of 24/year), the majority in adults (92%). One thousand five hundred sixty-seven heart transplants have been performed, (92% in adults) at an average of 78 per year, including a limited experience with heterotopic heart transplantation.<sup>3,4</sup> Combined heart-lung transplants started in 1990, with a total of 57 adult and 10 pediatric procedures.

Argentina has pioneered lobar lung transplants and reduced lung grafts. Approximately 10% of heart transplant recipients suffer from chronic Chagasic cardiomyopathy.<sup>3</sup> During most recent years, there has been an increasing utilization of short- and long-term ventricular assist devices in addition to Extra Corporeal Membrane Oxygenation in children and adults as a bridge to transplant or recovery. Accepted regulations for heart and lung organ allocation have been developed by local expert committees, based on the clinical severity and regional scores. The United Network for Organ Sharing Lung Allocation Score is not used in our country and a local expert committee developed a risk index for lung disease, based on etiology, mortality risk factors, and posttransplant survival. Patient and graft survivals are shown in Figure 2.

## KIDNEY TRANSPLANTATION

The first kidney transplant has been performed in 1957. Since 1998, a total number of 15774 kidneys have been

Received 4 January 2018. Revision received 9 November 2017.

Accepted 22 December 2017.

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The authors declare no conflicts of interest.

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ISSN: 0041-1337/18/10206-0883

DOI: 10.1097/TP.0000000000002172



**FIGURE 1.** Argentina geographical setting. Image credit: [https://commons.wikimedia.org/wiki/File:ARG\\_orthographic\\_\(%2Ball-claims\).svg](https://commons.wikimedia.org/wiki/File:ARG_orthographic_(%2Ball-claims).svg).

transplanted into adult and pediatric recipients; the rate of deceased donation is 75%.

Currently, Argentina has 29000 patients on different modes of dialysis. Of those, 6000 fulfill the requirements to be placed on the kidney transplant list; however, only 1300 transplants have been performed yearly. Twenty-five percent of patients requiring dialysis are older than 60 years. To assure organ and transplant availability in this age group, the INCUCAI created the “Old for Old” program in 2010 prioritizing the placement of older kidneys into older recipients.<sup>2</sup> There are active programs performing heart, liver, and intestinal transplant combined with kidney transplant with results comparable to international experiences. In 2015, the INCUCAI approved paired exchange programs, with excellent results.<sup>2</sup> Overall patient survivals for kidney transplant are shown in Figures 3A and B.

## LIVER TRANSPLANTATION

The first adult liver transplant in Argentina was performed in 1988. During the same year, the first pediatric liver transplant in South America has been performed<sup>5</sup>; first split liver transplant was performed in 1990,<sup>6,7</sup> first pediatric living

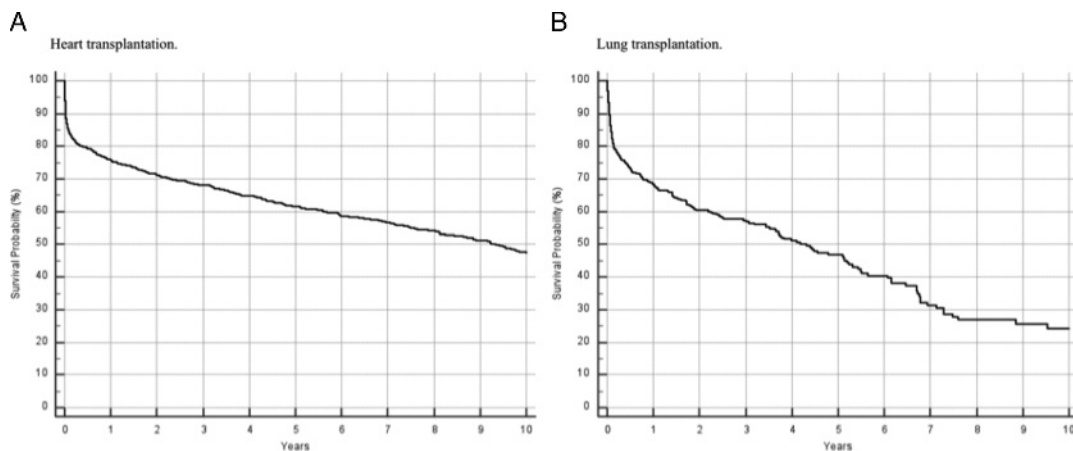
donor liver transplant in 1992,<sup>5</sup> the first combined liver/kidney in 1996, the first adult living donor liver transplant with a left lobe in 1998,<sup>6</sup> the first adult living donor liver transplant with a right lobe in 2001, the first domino liver transplantation in 2003,<sup>1</sup> the first liver/heart in 2006, the first split/domino liver transplant from a single deceased donor deceased donor in 2014,<sup>8</sup> and the first dual graft liver transplant in 2016.<sup>9</sup> With the evolution of all possible procedures, more than 4700 liver transplants have been performed, the majority from deceased donors (89%); living donor livers were transplanted into adults (26%) and pediatric (74%) recipients, respectively; at average, 330 liver transplants are being performed/year. Liver allocation is based on the Pediatric End-Stage Liver Disease-Model for End-stage Liver Disease (PELD-MELD) system. Overall national patient survivals are shown in Figures 3C and D.

## PANCREAS TRANSPLANTATION

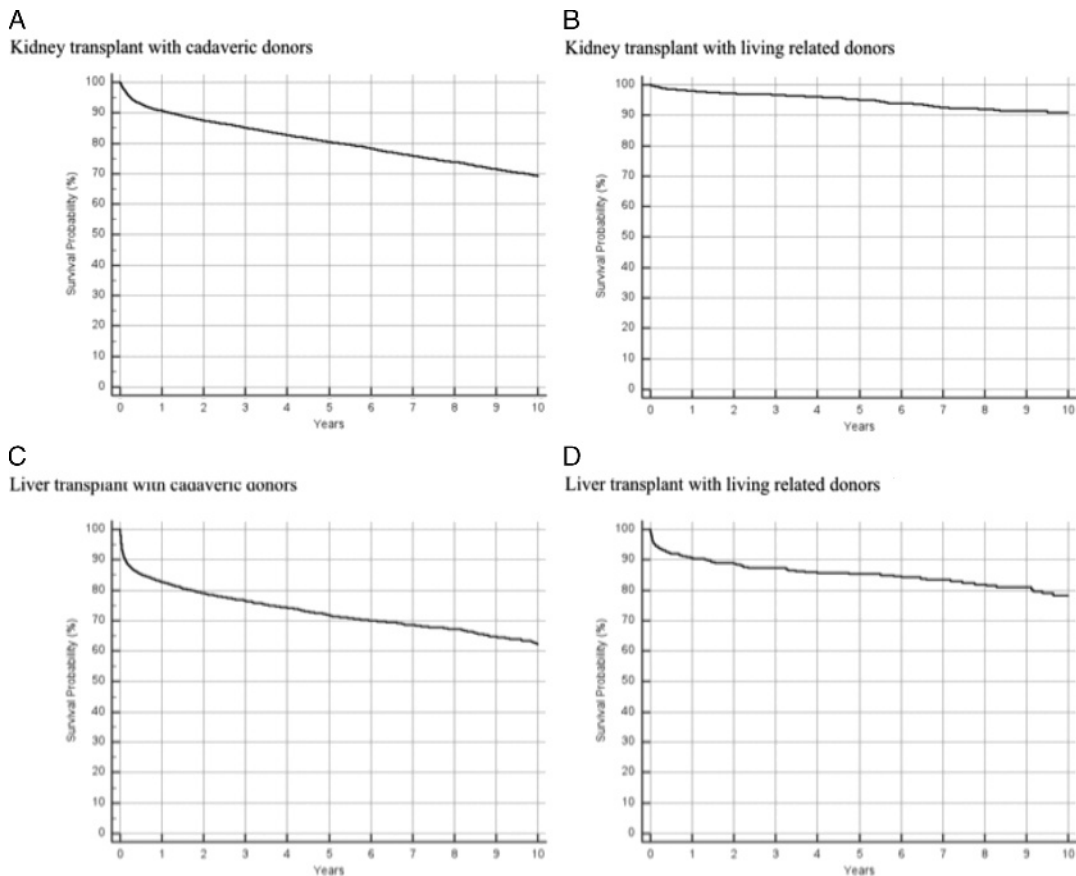
The first pancreas transplant was performed in 1994.<sup>10</sup> After initial pancreas transplant volumes of 7 per year until 2006, new programs started to increase the applicability and indications by offering not only kidney-pancreas but also isolated pancreas and pancreas after kidney transplants, in addition to recognizing the benefit for pancreas transplantation in candidates with type 2 diabetes.<sup>11</sup> Since then, the number of pancreas transplants has increased to an average of 56 per year, with a total of 792 procedures since 1994. Islets transplants are performed at a single institution; the islet program started in 1995, 27 islets transplants have been reported until 2005, when the program discontinued. Nationwide, patient survivals are 76% and 67% by 5 and 10 years, respectively.

## INTESTINAL TRANSPLANTATION

A first attempt for intestinal transplantation had been pursued in 1999.<sup>10</sup> The first intestinal failure, rehabilitation, and transplant unit was established in 2006.<sup>12</sup> First successful multivisceral transplants were performed in 2006, first pediatric combined liver-intestine in 2007,<sup>12</sup> modified multivisceral (stomach, duodenum, pancreas, and intestine while preserving the recipient’s liver) in 2013; the first combined liver-intestine transplant into an adult recipient has been carried out in 2017. A second intestinal transplant program has



**FIGURE 2.** Overall (pediatrics and adults) intrathoracic transplants patient survival (1998-2017).



**FIGURE 3.** Overall (pediatrics and adults) kidney and liver transplants patient survival (1998-2017).

opened in 2008 in Buenos Aires. Since 2006, 60 procedures including isolated intestinal transplants have been performed (48 and 12, respectively, in each program, including 41 pediatric and 19 adult intestinal transplants). Regulations for listing, allocation, and the accreditation and reaccreditation of programs have been established. At this time, 47 isolated, 6 combined liver-intestine, 6 multivisceral, and 1 modified multivisceral transplant have been performed. Patient survival rates are 56% and 42% by 5 and 10 years, respectively.

### BASIC SCIENCE IN TRANSPLANTATION

Transplant-related basic science has a more than 25-year history at public and private institutions in Argentina. Initial work focused on ischemia-reperfusion injury, extracorporeal liver support, islet transplants, and the development of microsurgical procedures. In 2006, facilities added translational approaches and projects have been increasingly funded by the Argentinean Ministry of Sciences in addition to International societies including INCUCAI, Argentinean Transplant Society, and Latin American and Caribbean Transplant Society that support scientific projects, research institutes, scientists, and students, all contributing to increasing academic productivity and quality.<sup>13,14</sup>

### GAINING TRANSPLANT EXPERTISE

Pioneer transplant surgeons trained mainly in Europe and the United States. Some surgeons and physicians continue their training overseas; however, transplant fellowships have

been initiated in Argentina in the 1990s. Since then, well-recognized transplant training programs evolved and have been endorsed by local, regional, and international associations and are becoming reference training centers mainly for Spanish-speaking countries in the region.

### CHALLENGES

Argentina is actively working on (i) developing new programs for using donors after circulatory death, and (ii) utilizing of ex vivo organ perfusion devices and implementing vascular composite all (VCA) grafts, including uterus transplants.

Moving forward, authorities of the different health administration systems and physicians start to understand not only the medical but also clinical advantages of organ transplantation as the treatment of choice for end-stage organ failure. Improving the currently low organ donation rates continues to be a challenge and needs to be addressed to meet the goal of achieving self-sufficiency that will reduce mortality on the waiting lists.

### ACKNOWLEDGMENTS

The authors thank Francisco Pattin MD, for his support literature search and editing of the article and to Miss Patricia Casetta for her support as the official English translator.

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## Research Highlights



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## The Impact of Sex on Alloimmunity

Lau A, West L, Tullius SG. *Trends Immunol*. 2018;39:407–418.

**T**ransplantation outcomes are affected by the sex of donor and recipients, aspects that are not always recognized when allocating organs. In the recent publication in *Trends in Immunology*, the authors collected evidences and present potential mechanisms driving sex-specific immune responses impacting sex-specific transplant outcomes.

In kidney transplantation, female, as well as pediatric, donor kidneys have an inferior survival compared with male donors. Those aspects are particularly pronounced in male recipients and had in the past been attributed mainly to lower nephron numbers. However, grafts from female donors also have higher rates of acute rejections, particularly evident in HLA-mismatched transplants.

Estrogen promotes proinflammatory cytokine production and Toll-like receptor expression to increase T cell activation by female antigen-presenting cells which may augment both acute and chronic rejection rates. In contrast, testosterone inhibits proinflammatory cytokine production and decreases both T lymphocyte receptor expression and T-cell activation by male antigen presenting cells, which may result in lower rates of acute and chronic rejection. Additional

contributions may result from sex chromosome-mediated effects on immune functions.

In an age-dependent fashion, female recipients of male donor kidneys experience higher rates of graft loss compared with male recipients. This effect has largely been attributed to female-specific immune responses against male minor histocompatibility antigens. Interestingly, graft failure rates in women older than 45 years are reduced, suggesting a hormonal influence in premenopausal women.

Pregnancy levels of estrogen and progesterone cause increased regulatory T cell numbers in female recipients. Moreover, high levels of estrogen in pregnancy inhibit B-cell precursor development while promoting B-cell survival in female recipients. These changes in cellular and humoral immunity may contribute to lower graft rejection rates in pregnancy relative to nonpregnant female recipients.

Premenopausal levels of estrogen and progesterone in female recipients may cause increased levels of proinflammatory type 1 T-helper cell cytokines and higher levels of B cells and antibodies relative to male recipients. In addition, females who receive male donor grafts mount cellular and humoral immune responses against the H-Y antigen, a male-specific minor histocompatibility antigen linked to the Y chromosome. These factors likely contribute to higher rates of graft rejection in premenopausal female.

Postmenopausal levels of estrogen and progesterone in female recipients cause decreased proinflammatory cytokine production and reduced B-cell survival linked to less robust cellular and humoral immune responses that may cause lower graft rejection rates in postmenopausal female recipients relative to premenopausal female recipients.

Received 5 April 2018. Revision received 9 April 2018.

Accepted 10 April 2018.

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The author declares no conflicts of interest.

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ISSN: 0041-1337/18/0000-0000

DOI: 10.1097/TP.0000000000002231