Organ Donation and Transplantation in Latvia

Ieva Ziedina, MD, PhD,[1,2] Janis Jushinskis, MD, PhD,[1,2] Sandra Lejniece, MD, PhD,[1,3] and Eva Strike, MD, PhD[1,2]

Latvia is a country located in Northern Europe bordering the Baltic Sea (Figure 1). In 2018, Latvia celebrated a 100 years since as an independent state. Riga, Latvia's capital and the biggest city in the Baltics, was founded already in 1201.

The World War II brought occupation under both, German and Soviets, and de-facto freedom was only regained in 1991. Joining NATO and the European Union (EU) in 2004 have been recent historic events. The population of Latvia has declined from 2.5 to 1.9 million since the independence from the Soviet Union. Unique in the EU, the majority of researchers (52%) in Latvia is female.[2]The 2018 annual GNP was € 29.4 billion. With a growth rate of 4.8%, Latvia is a leader among EU countries.[3]

TRANSPLANT ACTIVITIES

Solid organ transplantation started in 1973[4] with live donor kidney transplantation (father to his 15-y-old daughter) at Pauls Stradins Clinical University Hospital in Riga. This institution remains the only organ transplantation center in Latvia and is currently offering adult kidney, pancreas, heart, and liver transplants in addition to pediatric kidney and heart transplants; lung and intestinal transplants are currently not offered in Latvia. Riga East Clinical University Hospital is performing bone marrow.

LEGAL FRAMEWORK OF ORGAN DONATION

The law "On the Protection of the Body of Deceased Human Beings and the Use of Human Tissues and Organs in Medicine" has been adopted in 1992,[5] only a year after the de-facto independence from the Soviet Union. Deceased donation in Latvia is based on a presumed consent with the possibility to register as a "nondonor". Even though the legal framework is clear, family consent is usually obtained before organ procurement.

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[1] Riga Stradins University, Riga, Latvia.

[2] Pauls Stradins Clinical University Hospital, Riga, Latvia.

[3] Riga East Clinical University Hospital, Riga, Latvia.

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I.Z., J.J., S.L., and E.S. participated in the writing of the article and in data analysis.

Corespondence: Ieva Ziedina, Pauls Stradins Clinical University Hospital, Pilsonu St 13, Riga, LV 1002, Latvia. (ieva.ziedina@stradini.lv).

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SOLID ORGAN TRANSPLANTATION

Deceased organ donor rates have dropped from 17.3 pmp in 2000 to 12.3 pmp in 2017.[6] There are approximately 6 donors pmp after cardiocirculatory death (DCD) annually. Living donor kidney transplants have been reinitiated in 2007 and rates have increased up to 6.7 pmp in 2017[6] (Figure 2). Close to three quarters (74%) of living donors are genetically related, the majority being parents; the remaining 26% of living donors are emotionally related, the majority being spouses. To raise awareness for organ donation, Latvia is participating in the EU project on "Training and social awareness for increasing organ donation in the EU and neighboring countries". Since 2017, transplant coordinators are localized in all university hospitals in Riga in addition to major regional hospitals.

As of January 2019, 2023 kidney, 27 heart, 4 pancreas, and 7 liver transplants have been performed in Latvia.

The incidence of renal replacement therapy has plateaued during the last years with approximately 97 pmp (2015).[7] The prevalence of patients on renal replacement therapy in Latvia has increased at the same time (from 450 pmp in 2013 to 540 pmp in 2018). In absolute numbers, there have been 1058 patients on renal replacement therapy in 2017 including 55% with a functioning kidney transplant, 36% have been on hemo-, and 9% on peritoneal dialysis.

Annually, 12% of all patients on dialysis are listed for kidney transplantation. Pre-emptive kidney transplants are rare. Historically, most kidney transplants have been from deceased donors; however, recently live donor kidney transplants have increased rapidly. While live donor kidney transplants contributed with only 8% in 2012, rates have increased to 25% in 2017.[6] It is worth noting that the live donor kidney transplant program that started in 1973 had been on hold as deceased donor transplant rates had increased. However, with a drop of deceased kidney donors from 18.7 pmp in 2007 to 13 pmp in 2008, the live donor kidney program has been reactivated reaching 6.7 pmp in 2017.[6]

Kidney transplants from living donors across HLA barriers have been performed since 2011; ABO-incompatible kidney transplantations since 2012. The protocol for ABO incompatible transplantation includes a single dose of rituximab (300 mg/m^2) and plasmapheresis or immunoadsorption aiming at anti-ABO titers of less than 1:8. Living kidney donor exchange programs started in May 2013 and have thus far been carried out as paired donations.

Delayed graft functions in deceased donor kidney transplants vary from 10% to 30% and are mainly linked to donor age and prolonged ischemia. Biopsy proven acute

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FIGURE 1. Location of Latvia in the European Union.[1]

rejection rates had been as high as 30% but have dropped to 18% since utilizing tacrolimus as an initial maintenance immunosuppressant. Short and long-term graft and patient survival rates are comparable to other European countries; 20% of all kidney transplantations are retransplantations.[8]

The heart transplant program in Latvia has started in 2002 with rates of 0.5 pmp in 2017.[6]

The first successful liver transplantation in Latvia has been performed in 2011.[6] Until 2017, liver transplant activities have been on a hiatus and patients had been listed at other European Centers (mainly Tartu, Estonia), returning to Latvia for post-transplant care. Liver transplant activities resumed in 2018 at Paula Stradina Clinical University Hospital and 6 liver transplants (including one urgent retransplantation) have been performed thus far reaching 3.15 pmp.

The first simultaneous kidney–pancreas transplant has been performed in 2008;[6] however, the procedure has been infrequent and there is currently no active program. Multivisceral or vascular composite tissue transplantations are currently not performed in Latvia.

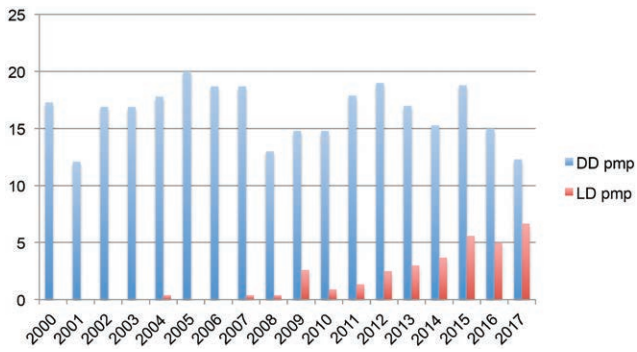

FIGURE 2. Deceased and living organ donor rates in Latvia pmp.

Lifelong post-transplant immunosuppression is supported by the government.

BONE MARROW TRANSPLANTATION

Hematopoietic stem cell transplantation (HSCT) has been started in 2000 with the first autologous HSCT for a patient with non-Hodgkin's lymphoma (NHL). High-dose chemotherapy in combination with autologous HSCT has been implemented in 2001. To date, 280 autologous HSCT have been performed for patients with NHL, Hodgkin's disease, and multiple myeloma.

Autologous HSCT have been performed for the first time in 2019 for 2 patients with testicular nonseminoma and one patient with a connective tissue disease.

The first allogenic HSCT has been performed in 2006. Allogeneic HSCT in Latvia are limited to related donor/recipients. Patients requiring a nonrelated donor or pediatric recipients will need to travel abroad. Since 2006, 30 allogenic HSCT have been performed in patients with acute leukemia (24), severe aplastic anemia (4), and chronic myeloid leukemia (2).

CHALLENGES AND OPPORTUNITIES

Transplant numbers continue to increase in Latvia. For many years, Latvia has participated in the donor network of the Baltic states (Balt-transplant). Recently, Estonia has joined Scandiatransplant and Latvia continues to cooperate for kidney and heart donations with Lithuania. Close co-operations continue also with the National Center of Pathology, an Affiliate of Vilnius University Hospital Santaros Klinikos.

One of the main current challenges is the missing accreditation of our HLA laboratory by the European Federation for Immunogenetics. An achievement is our active living kidney donor exchange program.

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Research Highlights

Laura Barisoni[1] and Xunrong Luo[2]

Clinical-grade Computational Pathology Using Weakly Supervised Deep Learning on Whole Slide Images

Campanella G, Hanna MG, Geneslaw L, et al. *Nat Med.* 2019; 25:1301–1309.

Computational image analysis is an evolving field that relies on digital whole slide imaging and computer algorithms to create decision support tools for pathologists, clinicians, researchers, and patients. The immediate goal is to enhance the efficiency and accuracy of morphologic assessment, while enabling generalizability, which should result in better global patient care. While this science has been operating for some time in radiology, it is in its infancy in pathology. Generating such computer algorithms has so far relied on small, supervised (manually annotated) datasets for deep machine learning and training. The application of such algorithms to large-scale unsupervised datasets, however, is often problematic due to wide variances of clinical samples typically not captured by small training datasets. In addressing this challenge, Campanella et al[1] presented a new framework for training at a very large scale based on "multiple instance learning," aiming to train a classification model in a weakly supervised manner. This process employs information from anatomic pathology laboratory information system and/or electronic health records, and involves the following several steps: (1) tiling of the entire slide image; (2) training at the tile level and ranking the tiles according to their probability of being positive; (3) integrating information across the entire slide using a recurrent neural network; and (4) correlating with or reporting the final classification result. To test the validity of this approach, the authors used a binary system (presence or absence of tumors on the whole slide images), with the goal of achieving 100% sensitivity while maximizing the area under the curve of the receiver operating characteristic curve. Achieving 100% sensitivity would allow such an algorithm to be used as an effective digital screening tool, minimizing the work load of pathologists while not missing any potential positive cases. The authors tested 3 large datasets involving prostate cancer, basal cell carcinoma, and breast cancer metastasis to axillary lymph nodes, totaling 44 732 whole slide images from 15 187 patients, all without any data curation, were tested. To further address generalizability, the datasets were provided by different sites with the use of different slide scanners. This framework achieved an area under the curve of >0.98 for all cancer types, excluding 65%–75% of negative slides while retaining 100% sensitivity.

Such an approach could be applied to transplant clinical care. For example, optimal caring for organ recipients is often critically dependent on our ability to timely detect immunological activities and accurately discern nature, mechanisms, and etiology of structural changes from implant, for cause or protocol biopsies.[2] Implementing such a computational decision support system would therefore significantly enhance our efficiency and precision in our clinical practices. Thrre of the following advances of such a system would be highly advantageous for its application in transplantation: (1) deep learning annotation and classification of tissue structural changes predictive of mechanisms and outcome; (2) algorithms that efficiently assess continuous variables rather than binary outputs; and (3) the ability to report the final classification also as continuous, quantifiable outputs. The framework demonstrated here exhibits the ability to train accurate classification models at an unprecedently large scale, providing a solid basis for future improvements, and development of computational decision support systems for practical clinical utilities.

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[1] Department of Pathology, Duke University School of Medicine, Durham, NC.

[2] Division of Nephrology, Department of Medicine, Duke University School of Medicine, Durham, NC.

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