CLÍNIC BARCELONA
Hospital Universitari

IDOTCOVID
International Database on Organ Donation and Transplantation - COVID19

International Database on Organ Donation and Transplantation - COVID19

ETHICAL IRB PROTOCOL

IDIBAPS
Institut D'Investigacions Biomèdiques August Pi i Sunyer

DTI
DONATION & TRANSPLANTATION INSTITUTE

UNIVERSITAT DE BARCELONA

Study Title

International Database on Organ Donation and Transplantation - COVID19

Principal Investigators

- Fritz Diekmann
  - Nephrology and Kidney Transplant Department, Hospital Clínic Barcelona, Spain
    - fdiekman@clinic.cat
- Pedro Ventura-Aguiar
  - Nephrology and Kidney Transplant Department, Hospital Clínic Barcelona, Spain
    - pventura@clinic.cat
- Constantino Fondevila
  - Hepatobiliopancreatic Surgery Department, Hospital Clínic Barcelona, Spain
    - cfonde@clinic.cat
- Marti Manyalich
  - Transplant Advisor, Medical Direction, Hospital Clinic
    - marti.manyalich@dtifoundation.com]

Colaborators

- Maria Paula
  - Executive Director, Donation and Transplantation Institute
- Marían Irazabal
  - Project Coordinator, Donation and Transplantation Institute
- Chloe Ballesté
  - Associate Professor, Department of Surgery and Surgical Specialties, Faculty of Medicine, Barcelona University
- Entela Kondi
  - Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS);
- Enric Montagud-Marrahí
  - Nephrology and Kidney Transplant Department, Hospital Clínic Barcelona, Spain

Technical Committee

- Sergio Montagudo
  - My name is Mira, Barcelona, Spain
- Vesa Manninen
  - My name is Mira, Barcelona, Spain

Study Promotor

IDIBAPS - Institut d'Investigacions Biomèdiques August Pi i Sunyer.

Carrer del Rosselló, 149

08036 Barcelona, Spain

On site study details:

Principal investigator

Pedro Ventura Aguiar

Nephrology and Kidney Transplant Department

Hospital Clínic Barcelona

Carrer Villarroel, 170

09036, Barcelona, Spain

pventura@clinic.cat

Tel: +34 932 27 54 00

Background

Coronavirus Disease 2019 (COVID-19) is a novel viral disease caused by a coronavirus infection with a particular predominance of upper and lower respiratory tract symptoms. First diagnosed in China in late 2019, the virus has progressed to a state of pandemia, with countries in all 5 continents being affected. Up to date, there are more than 500.000 confirmed cases worldwide according to the WHO. In the general population, the reported case fatality rate is low, about 1-6%. However, most of the fatal cases have occurred in patients with advanced age or underlying medical comorbidities.

Viral infections often present atypically in solid organ transplant (SOT) recipients due to chronic immunosuppression (IS), and outcomes tend to be worse than those from the general population. In addition, there have been some risk factors associated with a worse outcome in COVID-19, such as hypertension and diabetes – both also frequent among SOT recipients.

There have been only 4 case reports of COVID-19 infection in SOT (2 heart, 2 kidney transplants) and one case series of 20 kidney transplant recipients, which reports a mortality up to 25%. Hence, there is a clear lack of evidence regarding epidemiology, disease presentation, antiviral treatments, influence of different immunosuppressors', immunosuppression reduction strategies, and, most importantly, outcomes.

The number of infected cases is increasing very fast in both Europe and North America, and is estimated to reach its peak during the following 2 months in both these continents. This area of the globe concentrates a very large number of SOT recipients. Moreover, there is still some uncertainty whether there is a seasonality of the virus and a second peak will present once again in Autumn/Winter.

Establishing treatment protocols in the current epidemic status of a novel disease is incompatible with awaiting for large multicentre retrospective studies that may be published in a later future. In order to provide evidence towards clinical decision making, transplant physicians need to be able to access a large database which enables them to compare outcomes using different strategies.

Hypothesis

H1: In the current pandemic with the new SARS-CoV2 coronavirus, disease presentation and severity of the infection are higher in patients receiving SOT.

H2: Immunosuppressive treatment and management in SARS-CoV2 infected patients will influence the evolution and cure of the disease.

Objectives

The main objectives of this project are the development of a tool that helps in the management of immunosuppression and the treatment of COVID19 infection in SOT recipients.

To achieve this, the following objectives have been designed to be developed in stages and progressively:

1. Creation of an international database that includes all SOT recipient patients with COVID19 infection (confirmed or suspected);
2. Inclusion of different clinical and analytical data with recognized prognostic factor in the general population;
3. Inclusion of treatment data, including management of immunosuppression and clinical outcomes;
4. Development of a Decision Support Algorithm (DSA) that can assist the scientific community in updating their treatment management and immunosuppression protocols in this high-risk population;

The DSA to be developed aims at aiding clinicians in their decision regarding treatment alternatives at the individual level. In summary, the Algorithm will be developed and trained based on the already available data on the database, with focus on pre-admission (i.e. recipient demographics, transplant type) and at admission (i.e. symptoms and biochemical values) data to explore and predict outcomes. The DSA will be developed in two phases (see methodology).

Once trained, upon introduction of a new patient on the database, expected outcomes according to the different therapeutic approaches will be provided to clinicians (i.e. expected outcomes according to withdrawal of immunosuppression or administration of COVID-19 therapeutic alternatives). This information will provide clinicians with real-time personalized information, and hopefully will aid in clinical decision making.

Study design

Multicenter international prospective observational study

Methodology

Participating Centers

Centers from all over the world performing follow-up of transplanted patients will be contacted and invited to participate in the study.

Upon agreement to participate, principal investigator (PI) from each collaborating center will be provided a login to the IDOTCOVID database (IDOTCOVID.org). Centers performing more than one type of SOT shall define a PI for each SOT, and a login be provided to each PI It is the PI's responsibility to introduce the data on the database.

The list of centers who agreed to participate and respective PI's is detailed in Appendix I and will be updated periodically.

Patient selection

All solid organ transplanted patients (Kidney, pancreas, liver, heart, lung, intestine/multivisceral, VCA [vascularized composite allograft]) with confirmed COVID19 infection will be included prospectively using electronic medical records.

Patients with negative test results but with clinical symptoms/radiologic findings suggestive of COVID19 infection will also be included.

Data Inclusion

Data to be included in the study concerns:

- Patient demographics: age, gender, race, country
- Patients' previous medical history: hypertension, diabetes, dyslipidemia, pulmonary disease, ischemic cardiac disease, or any other disease deemed significant (to be introduced as free-text);
- Transplant history: type of transplant, date of transplant, number of previous transplants, induction and maintenance immunosuppression, previous history of graft rejection, number of rejection episodes, date of last rejection episode, treatment of last rejection episode;
- Medication: Treatment with ACEI/ARB medication; Maintenance Immunosuppression;

- COVID19 history: Disease presentation symptoms, date of first symptoms, patient management (outpatient or hospital admission), hypertension at Hospital admission, hematological and biochemical values at hospital admission,gasometric values at hospital admission, pharmacological treatment for COVID19, management of immunosuppression during COVID19 infection, requirement for ICU and Invasive mechanical ventilation (IMV) or non-invasive mechanical ventilation (NIMV), date of ICU/MVI/NIMV, date of ICU/MVI/NIMV withdrawal, requirement for renal replacement therapy (RRT), type of RRT required, date of RRT indication, date of RRT withdrawal, patient and graft outcomes (functioning/alive vs failed/death), date of graft failure and/or date of patient death.

Decision Support Algorithm (DSA)

The development of the Machine Learning Algorithm will be performed using all the variables included on the database, including patients' demographics, transplant characteristics (including previous graft rejections), as well as all variables associated with the COVID-19 infection.

The DSA will be developed in two phases:

1. **Phase 1:** Based on medical experts' pre-defined and codified rules. This is expected to be performed on very short notice once the knowledge of the experts in the field has been captured and encoded.
2. **Phase 2:** Though Machine Learning, based on the different variables captured and the 'outcomes' of each of the cases, to identify those variables that have an impact on the result. In this case training of the model will be started once the initial 1000 cases have been reached and as new cases are added, it is retrained

The entire decision support system will be based on Ingenuous Pty Ltd software, which will be installed on the servers where the data shall be hosted. Said software called 'Intuition' uses as a data layer 'elasticsearch' which is a search engine specialized in search analysis in an unstructured data set. Both the web used to collect data through web forms and the software to support decisions will run on the same infrastructure, offering users who provide data a web application that integrates all the functionalities. A data scientist would access the data remotely and for a limited time for the development of the Machine Learning model.

Data management and protection

The treatment, communication and transfer of personal data of all participants will be in compliance with EU Regulation 2016/679 of the European Parliament and of the Council of April 27, 2016, being mandatory as of May 25, 2018 and the Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights.

The collected data will be collected identified only by a code, so no information will be included to identify the participants. Only the study doctor and his collaborators with the right of access to the source data (medical history), will be able to relate the data collected in the study to the patient's medical history. The study site is the controller with responsibility for all personal data collected from patients and contained in files, documents and medical records (including where these exist in electronic format), as well as for any other personal data it collects and processes as part of the study for the purpose of data retrieval.

Data will be introduced by study sites upon login to the IDOTCOVID.org webpage previously provided to study center.

The data can be entered either manually, through a batch, or through direct integration between data systems (in those who already have their data in other electronic registries). All communication is encrypted under pseudo-anonymization using a unique patient codification. Patient pseudo-anonymization will be performed by each center's principal investigator – PI's shall introduce a unique ID reference for each patient introduced, which shall be defined as per center PI's criteria. This ID (External ID) is different from unique ID attributed at first entry on the database (database ID). This External ID shall only be used for patient re-identification wCenters' PI'sshall it be required. Data managers will be unaware of External ID criteria decided by each center.

Data Servers

The data collection will be done through a web-based registry with the following characteristics (which will be regularly updated according to new security updates):

- Angular frontend (Angular 9)
- PHP backend (PHP 7.3.17)
- Communication between frontend and backend encrypted (SSL) and authorized using token mechanism
- MySQL database for data persistency (MySQL 5.7)

- Server infrastructure, can run on windows/Linux OS (Microsoft Dotnetcore framework 3.1)
- User interface can run on any HTML5 standard browser

The systems and products will be on several servers, under the same hosting service and always on the same network segment, used exclusively for the purpose of the IDOTCOVID service.

The services will be hosted in a cloud environment based in Spain and is offered by the company Dinahosting. Data is stored in the data center of the hosting company, being physically and digitally protected, and the data is backed up continuously.

There is a link with Dinahosting as a hosting service provider, which has the following certifications that ensure the security and integrity of data and services

- ISO 9001 quality
- ISO 27001 for information security
- ISO 22301 for business continuity
- ISO 14001 for the environment

Machine Learning Software

In addition to all the above for implementing the DSA the solution we would do an integration with the following elements:

- Intuition a product from Ingenuous Pty Ltd specialised in decisioning support solutions (Intuition 2020.1.6527.0)
- Elasticsearch, a non-SQL search engine (Elasticsearch 6.8.2)

'Ingenuous Pty Ltd' is a company specialized in systems for decision making. Its product called 'Intuition' would be used, which uses 'elasticsearch' as a data engine specialized in search analysis in an unstructured data set and widely used in specialized data analysis solutions. 'Ingenuous' has extensive experience in decision-making systems and data analysis, having developed an innovative product regarding the use of new technologies, while optimizing the resources used in the process, which is reflected in the cost competitive of the product, compared to others of the competition.

Data access

Study principal investigators and Technical Committee will have access to all data included on the webpage. Local PIs will have access to data included from their center. When required, and following an agreement, official national transplant organizations will have access to pseudo-anonymized data from their national cohort.

Upon request from any of the study collaborators, and only for research purposes of studies previously approved by local Ethical Investigation Review Boards, pseudo-anonymized individual patient data may be shared in an exportable database.

Data will be retained for a maximum of 10 years, and afterwards eliminated from the host service.

Patient informed consent

The present study is an observational study based on patient medical records, in which patient identification will be codified. In addition since individual patient identification will codified once introduced on the database, and only used as a cohort analysis and never as an independent case report which might lead to patient identification, similar to those used in registry analysis. Finally, under the current pandemia and workload pressure on health care workers, requirement for a patient informed consent is not viable. Hence, patient informed consent waiver is requested.

Expected Results

Worldwide there more than 5,000,000 transplanted patients. As a population at risk for infectious complications, obtaining a database and its decision support model may provide healthcare personnel with the scientific evidence necessary for their actions. In turn, this database will allow the optimization of immunosuppression in the early stages of the disease, being able to significantly reduce the number of patients that will require admission to Intensive Care Units. The present study represents an advance for action against new diseases or diseases of high incidence in a short period of time. The development of algorithms to aid clinical decision-making in risk populations will have a real-time benefit in information for patients and families.

Available Resources and Team Experience

This research team has the support and experience of DTI (Donation and Transplantation Institute). DTI Foundation has extensive experience in database management. DTI is responsible for IRODaT: The International Registry of Organ Donation and Transplantation, a database that provides information on donation and transplantation activity for each country worldwide. (http://www.irodat.org/). DTI also has a network of experts who will help and advise during the execution of the project. Among them, include Dr. Martí Manyalic (DTI President), Dr. María Paula Gómez, (Executive Director) and Dr. Chloe Ballesté (Director of International Cooperation and Development). It is important to note that this project has the experience and resources that IDIBAPS has. IDIBAPS is responsible for the registry of Living Donors Eulid and Edith, registries that were created with the financing of European Projects. Finally, this project has a technical team made up of the company My name is Mira. This consulting company aims to offer consulting services in technology sectors. Among the staff that will support this project, we must highlight Sergio Monteagudo, Computer Engineer Lead IT Consultant and Vesa Manninen, Lead Business Consultant who will support both the preparation tasks and the data processing.

Estimated Budget

The estimated cost for the development of the proposed project is € 250,000.

The budget includes the cost of the following sections:

- Database development;
- Application of said base to a web page with access in real time;
- Website maintenance;
- Statistical support for periodic reports of results to collaborating centers;
- Development of Machine Learning algorithm to help clinical decision;
- Marketing team for promotion and dissemination of the base;
- Logistical and administrative support;

Funding

There is no current funding for the IDOTCOVID. The project will be presented both to competitive calls, as well as to philanthropist donations.

APPENDIX I - Participating Centers

Center	Country	Principal Investigator	Organ
Hospital Clínic Barcelona	Spain	Fritz Diekmann	Kidney
Hospital Clínic Barcelona	Spain	Jordi Colmenero	Liver
Hospital Clínic Barcelona	Spain	Pedro Ventura	Pancreas
Hospital Clínic Barcelona	Spain	Elena Sandoval	Heart
Hospital Vall d'Hebron	Spain	Irene Bello	Lung
Hospital Santo António	Portugal	La Salete Martins	Kidney
Hospital Santo António	Portugal	La Salete Martins	Pancreas
Hospital do Rim	Brasil	Irene Noronha	Kidney
Hospital do Rim	Brasil	Irene Noronha	Pancreas
General Hospital of Southern Theater Command	China	Feng Huo	Kidney
UZ Brussels	Belgium	Karl Martin Wissing	Kidney
Belgium Transplantation Society	Belgium	Karl Martin Wissing	All organs
Hospital of the Padua Medical Center	Italy	Emmanuel Cozzi	Kidney
Asian Society of Transplantation	South Korea	Terence Kee	All Organs
Manchester University	United Kingdom	Tavakoli Afshin	Kidney
Iranian society of organ donatio	Iran	Katy Najafizadeh	All Organs
University Hospital Essen	Germany	Ute Eisenberger	Kidney
Hospital Universitario Fundacion Favaloro	Argentina	Gabriel Gondolesi	Kidney
ITAC Institute	Argentina	Pablo Uva	Pancreas
ITAC Institute	Argentina	Pablo Uva	Liver

Hospital Leforte	Brasil	Marcelo Perosa	Pancreas
Hospital Leforte	Brasil	Marcelo Perosa	Liver
Middle East Society for Organ Transplantation	Egypt	Refaat Kamel	All Organs